To assess the role of second resection in T1G3 bladder tumors

A thesis submitted for the degree of MCh,

Branch IV, Genitourinary surgery,

to Dr.M.G.R Medical University,

Chennai, Tamil Nadu

Acknowledgements

I thank God for giving me the opportunity and strength to complete this study.

I wish to express my deep gratitude to my guide, Dr Antony Devasia, for his encouragement and help during this period.

I sincerely thank Dr. Nitin Kekre for his invaluable inputs and suggestions.

I am extremely thankful to all my seniors and colleagues for the help and co-operation they extended during the course of the study.

I would like to thank Mr. Prasanna Samuel for his help in the statistical analysis.

I sincerely thank all the patients who participated in this study.

Last but not the least; I want to thank my family for all the support.

Title of the Abstract	:	To assess the role of second resection in T1G3 bladder tumors
Department	:	Department of Urology
Name of the candidate	:	Katumalla Francis Sridhar
Degree and subject	:	MCh, Branch IV, Genitourinary Surgery
Name of the guide	:	Dr. Antony Devasia

Aim: To assess the role of second resection in T1G3 bladder tumors

Material and Methods: This is a prospective study conducted in the Department of Urology, Christian Medical College, Vellore from April 2009 to December 2010. All T1G3 lesions were included in this study and variables like size, multifocality, characteristics of the lesions were analysed. Prevalence of second resection was calculated along with 95% CI. Chi square test was used to assess association between the categorical variables and tumor positivity in second resection. Thirty seven patients were diagnosed to have T1G3 disease, of which 27 had a second resection done. Hence, these patients were taken as the study group and the sample size.

Results: Fifty five percent of the lesions were solitary papillary and 09% were multiple papillary. All our resections had muscularis propria sampled at the end of the resection and separately sent for HPE which were tumor free. Thirty three percent of patients had residual disease at second resection and 3.7% were upstaged. Eighty five percent of the patients with solitary papillary lesions did not have any residual disease. When size also was considered, none of the patients with tumor size less than 3cms and solitary papillary lesions had a residual disease in second resection.

Conclusion: Patients with T1G3 tumors do not represent a homogenous group. Second TUR is recommended in patients with high grade T1 urothelial bladder carcinoma as it identifies residual disease and invasive disease. In our study, among the patients with solitary papillary lesion and size

<3cm, none had tumor in the second TUR and therefore the need for a second TUR is questionable in this group.

Contents

INTRODUCTION

INTRODUCTION

Transitional cell carcinoma (TCC) of the urinary bladder has a broad spectrum of disease course and treatment. The diagnosis and accurate staging of the tumor is an important initial step to determine the most appropriate management strategy.

Epidemiology:

TCC of the urinary bladder is the ninth most common cancer in worldwide cancer incidence. It is the 7th most common cancer in men and ranks 17th in women [1]. After prostate cancer, it is the second most common urological malignancy. The incidence of bladder cancer varies significantly all over the world, with Egypt, Eastern Europe, and North America having the highest incidence rates, and Asian countries the lowest rates [2]. More than 90% of new cases occur in people in the 6th decade, but the disease may occur in younger population as well [3]. The mean age of the patients diagnosed with bladder cancer is 69 years for men and 71 for women and the estimated ratio between men and women is 3.8/1 [4].

Risk factors:

Cigarette smoking and occupational exposure to urothelial carcinogens are the two most well-established risk factors for bladder tumors [5]. Fifty percent of bladder cancer in men and 35% in women is due to cigarette smoking [6]. Cigarette smokers have a 2 to 4 fold increased risk of bladder cancer compared to non-

smokers [7]. The incidence of urinary bladder cancer is directly related to the duration of smoking and the number of cigarettes smoked per day [8].

Sixteen to 24% of all the bladder cancers are due to occupational exposure to urothelial carcinogens and is the second most important risk factor [9]. Aromatic amines used in the chemical, rubber, and dye industries (eg, benzidine, 2-naphthylamine, 4-aminobiphenyl, o-toluidine, and 4-chloro-o-toluidine) and polycyclic aromatic hydrocarbons (PAHs) used in the aluminum, coal, and roofing industries are all known to be associated with the development of bladder cancer. An increased risk of bladder cancer has also been reported in painters, varnishers, and hairdressers [2].

Chronic urinary tract infections, cyclophosphamide use, and exposure to radiotherapy are the other known causes which are associated with urinary bladder malignancy [10]. Long term irritation of the bladder by indwelling catheters or stones, is related to development of squamous cell carcinoma of the bladder. Schistosomiasis is endemic in Egypt and the Middle East and is considered to be a definite cause of bladder cancer [11].

Inadequate consumption of fruits, vegetables, and certain vitamins may also play a role in the development of bladder cancer. Although it has been suggested that coffee consumption and artificial sweeteners may be associated with an increased risk of bladder cancer, results from epidemiologic studies investigating these agents have been inconclusive [2]. There is an increased risk of bladder cancer in individuals with a family history of cancer. A population-based,

family case control study found an almost 2-fold increased risk among first-degree relatives of patients with urothelial cell carcinoma [12].

Pathology:

The urinary tract extends from the renal pelvis to the urethra and is covered with transitional epithelium, also called the urothelium. Normal urothelium is three to seven layers thick. The external layer consists of large umbrella cells. The urothelium rests on the basal membrane of the lamina propria which consists of the subepithelial tissue and muscularis mucosa, followed by the muscularis propria (detrusor) and then the fat and the large venous plexus.

Transitional cell carcinoma bladder is the most common primary pathologic subtype of bladder cancer and is observed in >90% of tumours. Other subtypes are squamous cell carcinoma and adenocarcinoma and are less common and occur in approximately 5% and 1% of bladder cancers, respectively[2].

Classic TCC grows exophytically into the lumen of the urinary bladder and resembles swaying seaweed on cystoscopy. TCC can also grow as a sessile tumor in the bladder wall. A special variant of TCC is carcinoma in situ (CIS), a flat tumor, often multifocal and seen as velvety, red edematous patches on cystoscopy. There are three different kinds of CIS:

1. Primary CIS is CIS with no previous history of bladder cancer.

2. Secondary CIS is when CIS occurs with previously diagnosed TCC bladder.

3. Concomitant CIS implicates co-existing papillary or nodular tumor and CIS.

***Staging and Grading*:**

Stage and grade are significant prognostic factors for recurrence, progression, and survival. They are critical for the appropriate treatment and management of TCC bladder. The most widely used and universally accepted staging system is the tumour-node-metastases (TNM) system (Table 1).

The new classification for grading of non-invasive urothelial tumours was proposed by the World Health Organization (WHO) and the International Society of Urological Pathology (ISUP) and published by the WHO in 2004 (Table 2) [13]. It differentiates between papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade and high-grade urothelial carcinomas. The PUNLMP are lesions that do not have cytological features of malignancy but show normal urothelial cells in a papillary configuration. They have a negligible risk for progression, but still have a tendency to recur. The intermediate grade (grade 2), which was the subject of controversy in the 1973 WHO classification, has been eliminated [14].

Table 1: TNM staging of bladder cancer.

T: Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Ta Non-invasive papillary carcinoma

Tis Carcinoma in situ: ‘‘flat tumour’’

T1 Tumour invades subepithelial connective tissue

T2 Tumour invades muscle

T2a: Tumour invades superficial muscle (inner half)

T2b: Tumour invades deep muscle (outer half)

T3 Tumour invades perivesical tissue:

T3a: Microscopically

T3b: Macroscopically

T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

T4a: Tumour invades prostate, uterus, or vagina

T4b: Tumour invades pelvic wall or abdominal wall

N: Lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single lymph node ≤2 cm in greatest dimension

N2 Metastasis in a single lymph node >2 cm but not >5 cm in greatest dimension, or multiple lymph nodes, none >5 cm in greatest dimension

N3 Metastasis in a lymph node >5 cm in greatest dimension

M: Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Table 2 – World Health Organization (WHO) grading of urinary tumours in 1973 and 2004

WHO 1973

Urothelial papilloma

Grade 1: well differentiated

Grade 2: moderately differentiated

Grade 3: poorly differentiated

WHO 2004

Urothelial papilloma

PUNLMP

Low-grade papillary urothelial carcinoma

High-grade papillary urothelial carcinoma

PUNLMP = papillary urothelial neoplasm of low malignant potential.

Non Muscle Invasive Bladder Cancer (NMIBC):

Haematuria is the most common finding in non-muscle-invasive bladder tumours. Bladder irritation, dysuria, or urgency may be symptoms of CIS. Approximately 75–80% of bladder tumours present as non–muscle invasive disease and the remainder present as muscle-invasive disease. In NMIBC, approximately 70% present as Ta lesions, 20% as T1 lesions and 10% present as CIS or Tis lesions [10]. NMIBC represents a heterogeneous group of tumours with completely different oncologic outcomes. This heterogeneity in bladder tumors complicates the ability to compare the efficacy of different treatment modalities and thereby establish unified treatment recommendations. Therefore, risk stratification is imperative for classifying patients with similar risks of recurrence and progression, and it helps to determine the appropriate management strategies for each risk category [2].

T1G3:

T1G3 bladder tumor, a high grade lesion invading the lamina propria and yet to involve the muscularis propria, is highly malignant in the non-muscle invasive group [15]. T1G3 tumours have a high propensity to recur and progress to muscle invasion and are associated with a significant risk of metastasis and death. Eventhough T1G3 is classified as non muscle invasive tumor, about 15 – 20% progress to higher stage and nearly 75% develop recurrence [16]. 5% to 30% of patients with T1G3 ultimately die of bladder cancer within 5 – 10 years [15,17]. The biological characteristics of these tumors have been proved to be same as that of the muscle invasive transitional cell carcinoma (TCC) [16]. Nevertheless,

many of these tumors can be treated successfully with bladder preservation approaches. The dilemma facing the urologist is how best to treat these tumors in a timely manner so that the chances of bladder preservation and cancer control are maximized while the risks of overtreatment with radical therapy are minimized.

Factors predicting the poor prognosis of T1G3 tumors are multiple tumors, high grade lesions, larger size, sessile pattern, associated CIS and early recurrence of tumor after primary transurethral resection of bladder tumor (TURBT) [17,18]. A number of molecular and genetic prognostic factors have also been studied, but none of these have been validated prospectively [19]. Besides these, the duration of disease also influences the disease specific survival [20].

TURBT and intravesical therapy is now accepted as the reference standard for T1G3 tumors. The primary transurethral resection might leave residual disease, more so in multiple tumors, thereby increasing the risk of early tumor recurrence and stage progression even after intravesical therapy [21]. Second resection of T1G3 tumors may help to eradicate the residual disease and also to identify the early recurrence [21,22]. Keeping in mind the limitations of the current staging modalities, these tumors are understaged and a patient may receive inadequate treatment to a potentially curable disease [23]. Therefore a re-resection is routinely advised in all T1G3 tumors.

For all cases of newly diagnosed T1G3 TCC, a secondary TUR 4–6 wk after the primary TUR is strongly recommended. The advantages of a second TUR are many and discussed in detail. The morbidity associated with invasive re-

resection, the cost of the treatment and the delay in intravesical therapy questions whether re-resection is necessary in all T1G3 lesions [24]. Even after a satisfactory primary resection and a good muscle in the resected specimen, is it necessary to proceed with a re-resection?

REVIEW OF LITERATURE

REVIEW OF LITERATURE

T1G3 bladder cancer is associated with an aggressive course among superficial bladder tumors. They have a high propensity to recur and also to upstage to T2 disease. They are associated with a significant risk of metastasis and death. Literature shows long-term death rates as high as 34% [25]. An extremely variable 5-year progression rate ranging from 20 to 75% exists, probably due to the different risk subgroups in this spectrum of T1G3 [26]. Identifying these subgroups and the associated risk factors will help plan an effective management. The goal of the treatment of T1G3 bladder cancer is to decrease the mortality, ensure reduced morbidity and achieve a good quality of life. The dilemma facing the urologist is how best to treat these tumors in a timely manner so that the chances of bladder preservation and cancer control are maximized, while the risks of overtreatment with radical therapy are minimized [27].

To assess the role of conservative management in pT1G3 bladder cancer, a number of issues need to be considered:

- Is it really a pT1G3 tumor?
- The variability of pT1G3 bladder cancer
- The quality of clinical data

To confirm the stage and grade as pT1G3

The management protocol for patients with different stages of the disease (pTa, pT1 and pT2 or greater tumors) varies substantially [28]. Pathologists hold a key position in making a diagnosis and in commenting on the accurate stage & grade of a patient's tumor. They must be presented with suitable material along with relevant clinical information: the case is then best reviewed in the setting of a multidisciplinary uro-oncology meeting [29]. The pathologist must receive muscle-bearing specimens to determine whether muscle invasion has occurred. In 40% of 58 patients with apparently pT1 disease reviewed by Herr, muscle had not been included in the resection specimens from the referring hospital [30]. The uniformity of the pathologist's report, assuming adequate specimens, also needs to be accounted for. Evidence suggests that not only do experienced uro-pathologists vary in their diagnoses, they also may be inconsistent regarding the same specimen [31].Results in one study revealed that general pathologists tend to overstage tumors, but undergrade them [32]. A close liaison between the urologist and the pathologist, preferably in a multidisciplinary team meeting is hence important.

The variability of pT1G3 bladder cancer

Data on the untreated natural history of pT1G3 tumors is sparse, as these tumors generally require more than just a TURBT [33,34]. Heney and colleagues reported a progression rate of 48% at around 3 years in 27 patients with pT1G3 tumors [35]. This, however, was before the widespread use of intravesical treatments such as BCG. They were considered as tumors with high potential to

invade the muscle.It was noticed that the risk of progression and death from disease for patients with pT1G3 tumors is up to 10-fold greater than that for patients with other pTa and pT1 tumors [29]. As long-term data on the use of intravesical Bacillus Calmette-Gue´rin (BCG) has become available over the last twenty years, the idea of the so-called ‘‘rule of threes’’ has emerged, viz., of all the patients treated with BCG, approximately one third survive with their bladder intact, around a third require radical cystectomy, and around a third die of their disease [36]. This difference in outcome varies markedly from the very low progression rates seen with pTa tumors [35], to the relentlessly aggressive course of muscle-invasive disease. The dilemma, therefore, is to treat adequately, but not to over-treat. The outcome for patients with pT1G3 tumors also seems to be strongly influenced by the presence or absence of carcinoma in situ (CIS) [37]. The presence of associated CIS must therefore be carefully considered in the case for conservative treatment of a patient with a pT1G3 tumor.

The quality of clinical data

Patients may present with primary or recurrent tumors, with and without CIS, and with or without other factors that may influence the outcome, such as the presence of tumor in the prostatic urethra or the upper tracts [38]. Even with the information obtained from the systematic reviews and meta-analyses, at present, the ‘‘best’’ way to manage patients with pT1G3 bladder cancer is not clear.

PROGNOSTIC FACTORS

The important prognostic factors which help in predicting the outcome of the T1G3 tumors following the initial TURBT include early recurrence or new occurrence, multiplicity of the tumor lesions, size of the lesion, the presence of associated carcinoma in situ along with the T1 tumors, urothelial carcinoma involving the prostatic urethra or the ducts and the depth of the lamina propria involved [39]. T category and the grade of the tumor do not significantly influence the recurrence rate. Recurrence rate depends mainly on the multiplicity of tumors (single tumor, 51% recurrence at 5 years; multiple tumors, 91%), the previous recurrence rate, or the recurrence at 3 months [40]. In contrast, the grade and, to a lesser extent, the stage of disease is the most important prognostic factors for disease progression. The size of the tumor, the presence of tumor-associated CIS and the involvement of the prostatic urethra also carry a worse prognosis [41].

Increasing tumor size portends an increased risk for undetected infiltration of the lamina propria. The depth of the lamina propria involved is also a significant prognostic factor. The more the lamina propria appears infiltrated, the earlier are the chances of dissemination. Multifocality of the tumor carries a worse prognosis. The reasons for this are multiple. Multifocal tumors tend to be understaged, and the chances of complete resection decrease with the number of tumors [42]. Multifocality indicates the susceptibility of the entire urothelium to develop tumours (field change effect). There is thus a strong need for the close follow-up of the urethra and the upper urinary tract after cystectomy and of the bladder in patients selected for an organ preserving approach [42].

It has been seen in recent reports that patients with TaG3 tumors are also at high risk of life-long progression, not very different from that of patients with T1G3 tumors. Herr [43] followed 125 such patients for 15 years and observed progression in 39% and cancer related death in 26%. Similar data was reported by Lebret et al [44] where 32 patients with TaG3 tumors followed for 4 years had a 25% progression rate with 12% cancer-related deaths.

Apart from these unfavourable prognostic factors, the duration of the T1G3 disease also influences disease-specific survival. In a large study [45], on follow up for 8 years, 50% of the G3 patients either died from bladder cancer or developed muscle-invasive disease. After 15 years, more than half the patients with T1 disease developed a muscle-invasive tumor and a third died from metastatic carcinoma [46].

Molecular and genetic aspects such as altered expression of p53 have been implicated in the aggressive biological behavior of the bladder tumors. p53 mutations have been found in many cancers, including TCC. P53 overexpression is an independent predictive factor of recurrence for T1G3 bladder cancers. Retinoblastoma (Rb) gene was also evaluated as a possible predictive factor for the disease progression. Abnormal expression of p53 was found to be significantly responsible for the tumor progression [10].

As patients with T1G3 tumors have a life-long risk of progression some surgeons advocate cystectomy at the time of diagnosis [47,48]. The ideal course would be to find a compromise, i.e. to be as conservative as possible and at the same time avoid progression and death from bladder cancer [41]. Considering the

factors discussed, treatment may be improved by risk stratification and patient selection. Identifying the precise subset of patients with T1 bladder tumor who are at risk of disease progression is a major goal.

PREDICTING RECURRENCE AND PROGRESSION

This heterogeneity in bladder tumours complicates the ability to compare the efficacy of different treatment modalities and thereby establish unified treatment recommendations. Risk stratification is therefore imperative for classifying patients with similar risks of recurrence and progression. It also helps determine the appropriate management strategies for each risk category. To date, the European Organisation for Research and Treatment of Cancer (EORTC) risk tables are considered the most reliable tools for estimating progression and/or recurrence of NMIBC. The EORTC scoring system combines data on previous tumour recurrence rate, number of tumours, tumour diameter, T category and WHO grade, and the presence or absence of concomitant CIS to estimate the risk of recurrence and progression [49]. The EORTC scoring system is shown in Table 3, and the EORTC risk tables are shown in Table 4.

Table 3: European organization for research and treatment of cancer weighting used to calculate recurrence and progression scores [49]

FACTOR	RECURRENCE	PROGRESSION
Number of tumors		
Single	0	0
2 – 7	3	3
>8	6	3
Tumor diameter		
<3	0	0
≥3	3	3
Prior recurrence rate		
Primary	0	0
≤1 recurrence per year	2	2
>1 recurrence per year	4	2
Category		
Ta	0	0
T1	1	4
Carcinoma insitu		
No	0	0
Yes	1	4
Grade (1973 WHO)		
G1	0	0
G2	1	0
G3	2	5
Total Score	0 – 17	0 – 23

The main limitation of the EORTC risk tables is that the risk groups were based on patients who were mostly treated with older intravesical chemotherapy regimens [49]. The use of a single, immediate chemotherapeutic instillation, induction and maintenance BCG, and repeat transurethral resection of the bladder tumour (TURBT) were therefore not considered in the development of these tables. Improvements in chemotherapy administration, along with the increased use of BCG, may reduce the predictability of these tables. Notably, very few cases of CIS were included in the studies used as the basis for this scoring system and, hence, the EORTC tables may not accurately predict recurrence and progression in these patients.

Table 4: Probability of recurrence and progression according to score [49]

Recurrence score	Probability of recurrence at 1 yr (95% CI)	Probability of recurrence at 5 yrs (95% CI)
0	15% (10%,19%)	31% (24%, 37%)
1-4	24% (21%,26%)	46% (42%, 49%)
5-9	38% (35%,41%)	62% (58%, 65%)
10-17	61% (55%,67%)	78% (73%, 84%)
Progression score	**Probability of progression at 1 yr (95% CI)**	**Probabilityof progression at 5 yrs (95% CI)**
0	0.2% (00%,0.7%)	0.8% (0%, 1.7%)
1-4	01% (0.4%,1.6%)	06% (05%, 08%)
7-13	05% (04%,07%)	17% (14%, 20%)
14-23	17% (10%,24%)	45% (35%, 55%)

TREATMENT OPTIONS IN T1G3 BLADDER CANCER:

Transurethral Resection of Bladder Tumor

Transurethral resection of the bladder tumor (TURBT) is the first step in the initial treatment of bladder cancer. A TURBT is both diagnostic and therapeutic, and the procedure provides critical staging information. In the setting of a TURBT, the configuration (flat, sessile, or papillary), location (trigone, base, dome, or lateral walls), size (centimeters), and number of tumors should be noted. Tumors have to be completely resected and muscularis propria must be included in the specimen to ensure adequate resection, thorough histological

evaluation, and accurate clinical staging. Larger tumours must be resected separately in fractions, which include the exophytic part of the tumour, the underlying bladder wall with the detrusor muscle, and the edges of the resection area. The specimens from different fractions have to be referred to the pathologist in separate containers. Cauterization has to be avoided as much as possible during the resection to prevent tissue destruction. The pathologic report should specify the grade of the lesion & the depth of tumour invasion into the bladder wall. It must also and give information on whether the lamina propria and muscle are present in the specimen. A complete and correct TUR is essential for the prognosis of the patient.

Role of random biopsies

In the 1970s, the bladder cancer was believed to be a multifocal tumor with co-existing CIS distant from the primary tumour [40]. Biopsies from the normal looking mucosa were also recommended [50]. The role of random biopsies was questioned and in the recently published EAU guidelines: It is not routinely recommended.

Fujimoto *et al*. [51] and Van der Meijden *et al* [52] assessed the usefulness of random bladder biopsies of normal bladder mucosa after TURBT. Cancer was identified in only few biopsies and was thought to be un-warranted. If needed, multiple random biopsies were needed only in patients with multiple papillary tumors or in those with positive cytology results. Conversely, May *et al* [53] found that random bladder biopsies altered therapy in 7% of 1033 consecutive patients. In fact, in 14 patients, malignancy was identified in only the random biopsies and

not in the resection of the primary tumor. Importantly, however, these investigators excluded patients with small, primary, solitary bladder tumors. It was concluded that the patients with low- risk–appearing tumors and negative cytology results need not undergo random biopsy.

Role of Immediate Adjuvant Intravesical Chemotherapy

Clear consensus exists on the role of prophylactic chemotherapy in the first 6 hours after TUR. In an effort to reduce this risk, many trials have investigated the use of prophylactic or adjuvant intravesical therapy at the time of TURBT. Tolley *et al* [54] performed a multicenter, randomized trial of 502 patients with either Ta or T1 urothelial carcinoma. Those who received intravesical mitomycin C (MMC) within 24 hours of TURBT had a statistically significant decreased risk of tumor recurrence versus those who received placebo. Sylvester *et al*.[55] performed a meta-analysis on this and concluded that adjuvant intravesical therapy is the treatment of choice in patients with a single, low-grade superficial bladder tumor and should be the initial treatment (before subsequent intravesical BCG) in those with higher-risk bladder tumors. Multicenter, randomized, prospective studies demonstrate that the risk of recurrence can be reduced by half at 2 years and by 15% at 5 years with a single dose of adjuvant intravesical chemotherapy [54]. Routine use of prophylactic chemotherapy after TUR can thus be recommended. Contraindications to its use include very deep resections, bladder perforation, and prior documented allergic reaction. Although a wide variety of chemotherapeutic agents were used in the pooled trials (mitomycin C [MMC], doxorubicin, epirubicin, and thiotepa), the majority of

centres use MMC (40 mg in 40 cc of saline) as the prophylactic chemotherapeutic agent of choice.

A Second TURBT

T1G3 TCC of the bladder is associated with a significant risk of tumor progression and recurrence when transurethral resection (TUR) is the only treatment. Adjuvant immediate post TUR intravesical chemotherapy or maintenance immunotherapy can reduce this risk; however, long-term results of more than 15 years of follow-up indicate that almost 50% of the patients may end up in a radical surgery for the disease, or even die due to the cancer. The alternative to TUR is cystectomy at either the initial presentation or time of first recurrence. Although the results of this treatment strategy are encouraging, an unknown percentage of patients will lose their bladder and go on to experience all possible complications of urinary diversion unnecessarily- this option does seem to be overkill.

The concern of conservative treatment lies in the quality of TUR. With the available literature it is evident that a 'perfect TUR' cannot be performed on every patient, i.e. macroscopical clearance of the tumor from the bladder, separate resection of the tumor base, inclusion of the deep muscle in the specimen and separate biopsies of the borders of the resection area. Even in cases of a so-called 'correct TUR', a significant proportion of residual tumors is left behind and will be the source of local recurrence or progression. In addition, TUR specimens may be difficult to diagnose accurately, especially with respect to grade & stage.

Literature demonstrates that the routinely performed second TUR detects residual tumors of similar or higher stage in a significant percent of patients. The clinical implications of these findings can be quite significant, as the absence or presence of tumor may determine whether patients undergo conservative or aggressive treatment. Moreover, results of various retrospective studies support this suggestion [10,19]. The TUR after incomplete resection resulting from factors such as multiplicity, size, and location must be called repeat resection. If a second intervention is done to provide additional pathologic information for the muscularis propria, it has to be called re-staging TUR. The term second TUR is to be used only if the procedure is done after a complete and correct TUR. For all cases of newly diagnosed T1G3 TCC, a second TUR after the primary TUR is strongly recommended. In cases when a second TUR in a T1 is considered necessary to secure the completeness of the initial resection, the question arises: When should it be done? Several authors have shown that a second TUR can be performed safely a week after the first TUR [56], although proposed time frames range from 7 days to 3 months [56].The argument that this strategy should be based on the result of the second TUR indicates that this procedure should be done as early as possible. Thus, there is no reason to wait three months unless a second resection is not performed (as for cases with an intact mucosa and negative urine cytology) [56]. The advantages of performing a second TUR are manifold: It provides more accurate staging, detects and potentially clears the entire residual tumor and is helpful in prognostication. Second TUR reduces recurrence and also increases the recurrence-free interval and the progression-free survival.

Second TUR is of particular importance as the probability of understaging a T1G3 tumour ranges from 20–70%, depending on the presence of muscularis propria in the sample [27]. Herr [30] retrospectively evaluated the difference in the pathologic diagnoses between an initial TURBT and a second TURBT in 150 patients. The results of the second TURBT altered the treatment in 33% of the patients. Importantly, he noted the inability to correctly diagnose T1 tumors without muscle in the specimen. Of 23 patients with T1 lesions without muscle in the primary resection, 11 (49%) were upstaged to T2 lesions after review of the second TURBT specimen. Dutta *et al*. [57] similarly reported a 64% risk of understaging T1 lesions when muscle was absent versus 30% when muscle was present in the TURBT specimens. Kla¨n et al. demonstrated that patients who initially had a fractionated TUR had a reduced rate of residual tumor (36.7%) compared to patients in whom a separate resection biopsy of the tumor bed was not performed (56.3%) [56]. If muscle is absent from the initial TUR, a repeat resection is essential because of the high rate of understaging 27. Even with muscularis propria sampling at the first resection, several reports have proven occult T2 disease in up to 10% of second resections [27]. The high incidence of understaging at initial resection has been confirmed by analyzing the cystectomy specimens. In one study, 78 patients with non muscle invasive bladder cancer, who underwent cystectomy, 37% of the specimens showed muscle involvement [48]. As a second TUR often upstages T1 lesions and/ or provides additional pathologic information that can alter management decisions [27], repeat resection is indispensible in the T1G3 management armamentarium [27].

Divrik *et al* [58] report that doing a second TUR in patients with T1 tumors reduces the risk of bladder cancer recurrence and progression. A total of 210 patients were randomized to one of two groups. An initial TUR was performed in both groups, followed by a second TUR in one group only. This was done 2–6 weeks after the initial resection. Residual tumor was detected in 35 of 105 patients in the restaged group, and 8 patients were upstaged to T2. Recurrence, progression, and disease-free survival were followed in all patients, and significantly higher levels of recurrence and progression were seen in the patients who had not undergone a second TUR. Tumor recurrence occurred in 37 of 93 patients in the group who underwent a second TUR, and 70 of 98 patients in the other group, while progression was seen in 6.5% of patients in the second TUR group, compared with 23.5% of patients who did not undergo a second TUR. There were also more cancer- related deaths among the patients who did not undergo a second TUR - 11 deaths in 35 patients in this group, compared with 5 deaths in 30 patients in the group with a second TUR. Overall survival was 67.7% and 64.3% in the second TUR and without a second TUR groups respectively.

In addition to the diagnostic benefit, repeat TUR also has the ability to detect and potentially clear residual TCC. Since at least 27% of patients harbour residual tumour (with the highest reported rates of 62%) [27], repeat resections may have a therapeutic benefit. Zurkirchen *et al*. [59] retrospectively analyzed patients who underwent second TURBT within 6 weeks of their initial resection and found that 37% of patients with initial T1 bladder tumors had residual tumors on second resection. Grimm *et al*.[60] similarly analyzed retrospectively 83 patients who underwent a second TURBT. Residual tumor was found in 33% of cases, including 53% of those with initially diagnosed T1 bladder tumors. On univariate

analysis, both tumor stage and grade were identified as predictive for residual tumor on second TURBT. After 5 years, there was a significant decrease in disease-free survival between those who underwent a second TURBT and those who did not (63% and 40%, respectively). Brauers *et al*. [23] evaluated 42 patients' withT1 bladder tumors and found that 24% of patients were upstaged to T2 or CIS on second TURBT. Schips *et al*. [24] prospectively evaluated the findings at first and second TURBT for patients with high-grade T1 bladder tumors and reported residual disease in nearly 50% of patients. Both multifocality and tumor grade increased the risk of finding residual tumor on second TURBT.

Early repeat TURBT can be justified for the purposes of identifying understaged T2 tumors that would benefit from prompt surgery (cystectomy). In a series of 189 patients who underwent cystectomy within 3 months of diagnosis of muscle- invasive disease, there was a significantly better 5-year progression-free survival compared with those in whom cystectomy was performed in more than 3 months after diagnosis (55% and 34%, respectively) [19]. In summary, these studies show that the risk of upstaging on second TURBT is >30% if muscle is present in the specimen and even higher if muscle is not present [57.] Further, the risk of residual tumor on second TURBT is also significant. The risk for even solitary, papillary-appearing tumors is 24% to 27% [59].

An appreciated advantage of repeat TUR is prognostication. Although upstaging of T1G3 lesions to pT2 disease or higher automatically selects patients for radical therapy, Herr and colleagues showed that evidence of T1 disease on repeat TUR portends future muscle invasion [27]. Of 92 T1 patients with residual T1 disease at second resection, 82% progressed to muscle invasion by 5 yr. In

contrast, of 260 T1 patients who had no lamina propria invasion on a second TUR, only 19% progressed at 5 yr. Based on these results, residual T1 TCC on second TUR was deemed a negative prognostic indicator and a potential indication for immediate cystectomy in T1G3 patients. Due to these significant advantages, it is recommended that a second TURBT be considered for all patients with high-grade T1 urothelial TCC.

Additional Intravesical chemotherapy

Intravesical chemotherapy prevents recurrence but not progression, as confirmed by a meta-analysis comparing intravesical chemotherapy to TUR alone [61]. Two other meta analyses also demonstrated the efficacy of intravesical chemotherapy in decreasing the risk of tumour recurrence [62]. It is still controversial as to how long and how frequently intravesical chemotherapy instillations need to be given. From a systematic review of the literature of randomised clinical trials, comparing different schedules of intravesical chemotherapy instillations, one can only conclude that the ideal duration and intensity of the schedule remains undefined, because of conflicting data [63].

Adjuvant intravesical bacillus Calmette-Gue´rin immunotherapy

Adjuvant intravesical bacillus Calmette-Gue'rin´ (BCG) immunotherapy is the treatment of choice in T1G3 TCC. Standard induction therapy is of 6 weekly instillations after a second resection for a diagnosed T1G3 disease. The therapeutic benefit of BCG for T1G3 bladder cancers has been definitively established [64,65,66].

There is evidence to support the role of maintenance BCG therapy for T1G3 bladder cancer. In a prospective, randomised Southwest Oncology Group (SWOG) trial, Lamm et al evaluated the efficacy of induction plus maintenance BCG to induction BCG only in 384 patients with Ta or T1 disease at high risk of recurrence/ progression [27]. The maintenance protocol consisted of three weekly BCG instillations at 3 and 6 months post-TUR and semiannually thereafter, for 3 yr. Both 5-yr recurrence free survival (RFS) (60% vs. 41%, $p < 0.001$) and progression- free survival [PFS], (76% vs. 70%, $p = 0.04$) were improved with maintenance BCG.

MMC is a reasonable alternative with less side effects, but used only in situations where adjuvant BCG is contraindicated (allergy, intolerance to BCG, or immunosuppressed states) [27]. Patients experiencing severe side-effects from full-dose BCG may be considered for dose reduction, which may, however, compromise efficacy. Dose reductions of one-half to one-third BCG colony-forming units with improved side effect profiles without compromising on the efficacy and safety have been studied [67,68]. Recent reports by Martinez-Pineiro et al [69] and Yoneyama et al [70] have suggested worse outcomes with low-dose regimens in T1G3 patients, with trends towards reduced recurrence free survival. In T1G3, TCC dose reduced BCG regimens must be used with caution. Additional investigation of the role of reduced dose BCG is required.

Role of immediate or early cystectomy

The increased recurrence and progression rates associated with conservatively treated T1G3 TCC make cystectomy an option for some patients.

A number of advantages exist to this approach: a definitive opportunity for cure, and appropriate treatment of understaged lesions, to name a few. Though a second TUR refines local cancer staging, a high percentage of patients will still be understaged even after second TUR. Additionally, cystectomy enables lymphadenectomy. As up to 18% of T1 patients have positive lymph nodes, cystectomy can be both diagnostic and therapeutic for nodal metastases [27]. Lastly, cystectomy obviates the need for repeated intravesical therapies and simplifies follow-up.

Cystectomy for T1G3 TCC, however, also has a number of potential drawbacks. The perioperative mortality and morbidity rate following cystectomy (at 1–6% and 30% respectively) is not trivial [27]. Cystectomy may have a harmful impact on quality of life secondary to long-term changes in sexual, gastrointestinal, and genitourinary function. Finally, RC may be considered overtreatment for many patients as a conservative bladder-sparing approach with BCG is effective in around half the cases. An approach using reliable risk stratification is thus required to decide which patients to offer early cystectomy vs. where conservative treatment.

Other Treatment Modalities

The role of radiation therapy (RT) with or without chemotherapy for the treatment of T1G3 TCC is limited. Weiss et al retrospectively evaluated the impact of radiochemotherapy in 141 patients with T1G3 bladder cancer [71]. Of the 84 patients with T1G3 disease, 89% did not have tumour on restaging TUR six weeks after completion of radiochemotherapy. Long-term results, however,

showed that the 10-yr risk of progression for T1G3 patients was 29%. Vis a vis. BCG, however, the results of RT have not been as encouraging. In the largest randomized trial, Harland et al compared RT to conservative therapy (observation or intravesical BCG/MMC) in T1G3 TCC and found no difference in progression free survival [72]. Due to cost, inconvenience, potential for toxicity, and a lack of demonstrable benefit over conventional intravesical therapies, RT cannot be recommended for routine use as a bladder-preservation strategy.

Is A Second TUR A Must In All T1G3 Bladder Cancers?

Despite the existence of literature supporting a second TUR, there are a few investigators who still question this. Even after a satisfactory primary resection and presence of adequate muscle in the resected specimen, do we need to proceed with a second resection? Is there a sub group which can avoid a second TUR? The morbidity associated with invasive re-resection, the cost of the treatment and the delay in intravesical therapy makes one wonder if re-resection is required in all T1G3 lesions

T1G3 tumors are famed for their high progression and recurrence rates. A vast majority of this is due to incomplete primary resection and due to absence of muscle in the TURT specimen. Dutta *et al*. [57] reported a 64% risk of understaging T1 lesions when muscle was absent compared with 30% when muscle was present in the TURBT specimens.

Tumor architecture, (papillary or sessile, solitary or multifocality of the lesions) during the primary TURT are important prognostic factors for recurrence and progression of the disease. Solitary papillary lesions are deemed a good

prognostic factor over multiple papillary and sessile lesions [73]. Schips *et al*. [24] prospectively evaluated the findings at first and second TURBT for patients with high-grade T1 bladder tumors and also found residual disease in nearly 50% of patients.

Both multifocality and tumor grade increased the risk of finding residual tumor on second TURBT. Although 76% of patients with a solitary T1 lesion at first TURBT had a negative second TURBT, only 53% of those with multifocal T1 lesions had a negative repeat TURBT. Moreover, approximately 3/4ths of with papillary-appearing T1 lesions at first resection had a negative repeat TURBT compared with only 47% of those with solid-appearing T1 lesions. In another study, of 17 patients with a solitary T1G3 lesion who underwent a radical cystectomy after the primary TURBT, only one patient had a tumor in the resected specimen. The others were probably over treated [16]. It has also been felt that re-resection may not be required in all T1G3 lesions, and the primary TURBT can identify the subset of aggressive T1G3 tumors [74]. Invasion of lamina propria superficial to the muscularis mucosa (T1a) is considered a good prognostic factor as against the lamina propria deeper to muscularis mucosa. Involvement of muscularis mucosa in the lamina propria is considered T1b, and T1c is beyond the muscularis mucosa of lamina propria [75]. Orsola et al [76] commented on the European guidelines for NMIBC and suggested a second TUR in all T1 tumors.

In our institution we analysed a few characters of these T1G3 tumors and attempted to answer the question: Is a second TUR necessary in all T1G3 tumors even after a complete primary TUR?

AIM OF THE STUDY

AIM OF THE STUDY

To assess the role of second resection in T1G3 bladder tumors

MATERIAL AND METHODS

MATERIAL AND METHODS

This is a prospective study conducted in the Department of Urology, Christian Medical College, Vellore from April 2009 to December 2010. All the new patients who were diagnosed to have a space occupying lesion in the bladder and were planned for a transurethral resection of bladder tumor were assessed. The patient was explained in detail about the present study, the disease (Bladder cancer and T1G3 disease), and the management needed in the language best understood by the patient. Informed consent was taken for the study. Patient details, along with the clinical history and physical and systemic examinations were noted. Relevant blood and urine investigations and the radiological assessment were performed. Preanaesthetic evaluation was done for all the patients prior to the surgery.

The procedure was conducted in the operation room under general or regional anesthesia. A few of the patients needed obturator block to avoid obturator jerk and the complications associated with it. Detailed cystoscopic evaluation was carried out. The bladder lesions were meticulously assessed and all the features including the site, size, multiplicity, relation to the ureteric orifices and the appearance of the rest of the bladder mucosa were recorded. Endoscopic, video assisted transurethral resection of the bladder tumor was performed or supervised by a consultant. Karl Stroz / Wolf 26 fr active cutting resectoscopes were used for the procedure. All the visible lesions were resected and the tissue sent for histopathological examination. In all the subjects, after complete resection of the tumor macroscopically during the primary resection, deeper tissue with muscle was resected and sent separately for histopathological

examination. The pathologists' report of the inclusion of the muscularis propria in the specimen is the indication for a complete resection of the lesion.

A dedicated uropathologist assessed all the specimens sent and the presence of the malignancy along with the stage, grade, and the involvement of the muscularis propria was specifically mentioned. A second TUR was routinely performed in all the pT1G3 bladder tumors within 4 – 6 weeks. Resection was performed at the previous resection scar sites as documented by the earlier surgery records. and also at the doubtful areas. Presence of any new residual or recurrent disease is specifically looked for and the doubtful areas resected and sent for histopathological examination. The resected specimen was assessed for any residual tumor, its stage, grade and upstaging of the disease if any.

Statistical analysis:

Sample size: Sample Size was calculated using the following formula

$$N = \frac{4\,p\,q}{d^2}$$

- Outcome = Presence/absence of re-resection
- prevalence (p) of re-resection = 20%.
- q = 100-p : 100-20 = 80 %.
- precision = 10%

The required sample size to estimate a prevalence of 20% with a precision of 10% and with 95% CI was 70. This prospective study from April 2009 to December 2010, aims to include this sample size in the study, but being a prospective and time constrained thesis, all the patients in this time period were included for this thesis. A total of 37 patients were diagnosed to have T1G3 disease and of which only 27 had a second resection done. Hence, these 27 patients were taken as the study group and the sample size.

All the T1G3 lesions were included in this study and different variables like the size, multifocality, characteristics of the lesions would be analysed. Descriptive statistics was calculated for all study variables. Prevalence of re-resection was calculated along with 95% CI. Chi square test was used to assess association between the categorical variables and the T2 upstaging.

RESULTS

RESULTS

There were a total of 129 new patients who were diagnosed to have a bladder lesion from April 2009 to December 2010. There were 112 men (86.8%) and 17 women (13.2%) in this group. More than fifty percent of the patients were in the fifth and the sixth decades. (Fig 1). All of them underwent a transurethral resection of bladder tumor and the specimens sent for histopathological examination. Transitional cell carcinoma was diagnosed in 126 patients at different stages and grades (Table 1).

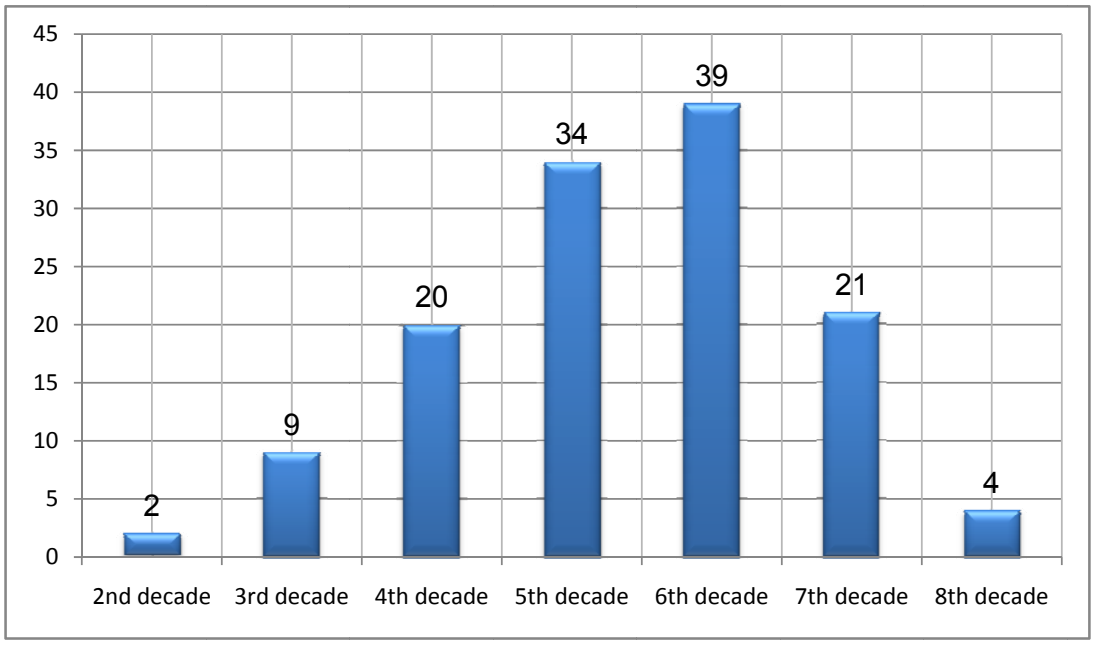

Figure 1: Age group of patients

Stage & Grade	No. of patients (%)
TaG1	Nil
TaG2	29 (23)
TaG3	17 (13.5)
T1G1	04 (3.1)
T1G2	08 (6.3)
T1G3	37 (29.3)
CIS	03 (2.3)
T2 disease	28 (22.2)

Table 1: Stage & Grade of TCC

Association of smoking was looked at in these patients with bladder lesions. None of the women had any association with tobacco. Out of the 129 patients with bladder lesions, 69 (53.48%) were regular smokers with variable cigarette pack years.

Of the 129 patients who underwent TURBT, 37 patients had T1G3 TCC bladder. Thirty of them were men and 7 were women. The mean age of the T1G3 patients was 57.3 years (37 – 75). Of these 37 patients with T1G3 lesions, 10 patients did not undergo a second resection. Two patients had multiple

comorbidities for a second procedure, 3 were not willing for a second procedure and 5 were lost to follow up. Out of 37, 27 patients had a second resection (Fig 2) and these patients are analyzed as the study group.

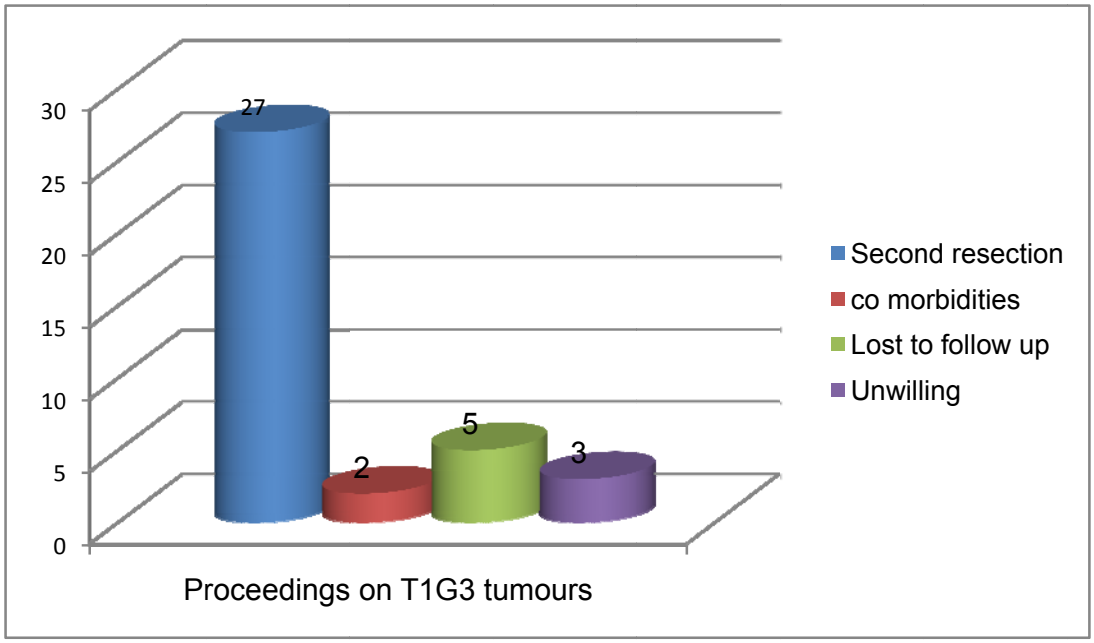

Fig 2: Proceedings on T1G3 tumours

The 27 patients who underwent a second resection in the group were analyzed in detail. The primary resection and the second resection along with variables like the site, size of the lesion, associated CIS, depth of invasion and the characteristics of the primary lesion were studied.

Of the 27 patients who underwent second resection, 22 were men and 5 were women. The mean age was 56.18 years (37 – 75 years). Three of these patients along with T1G3 had associated CIS (secondary CIS). Characteristics of the lesions have been assessed during the primary resection. They were

classified as solitary papillary, multiple papillary, sessile and multiple sessile lesions (Table 2).

Characteristics of the lesion	No. of patients (%)
Solitary papillary	15 (55.5)
Multiple papillary	09 (33.3)
Solitary sessile	03 (11.1)
Multiple sessile	Nil

Table 2: Characteristics of the primary lesion.

Most of these tumors were located on the lateral wall (Fig 3). When there were multiple tumors, the site of the largest tumor was considered. Twelve of these lesions were ≥3cm in size, and fifteen were < 3cm in size (Table 3)

Size of the lesion	No. of patients (%)
≥ 3cm	12 (44.4)
< 3cm	15 (56.6)

Table 3: Size of the lesions.

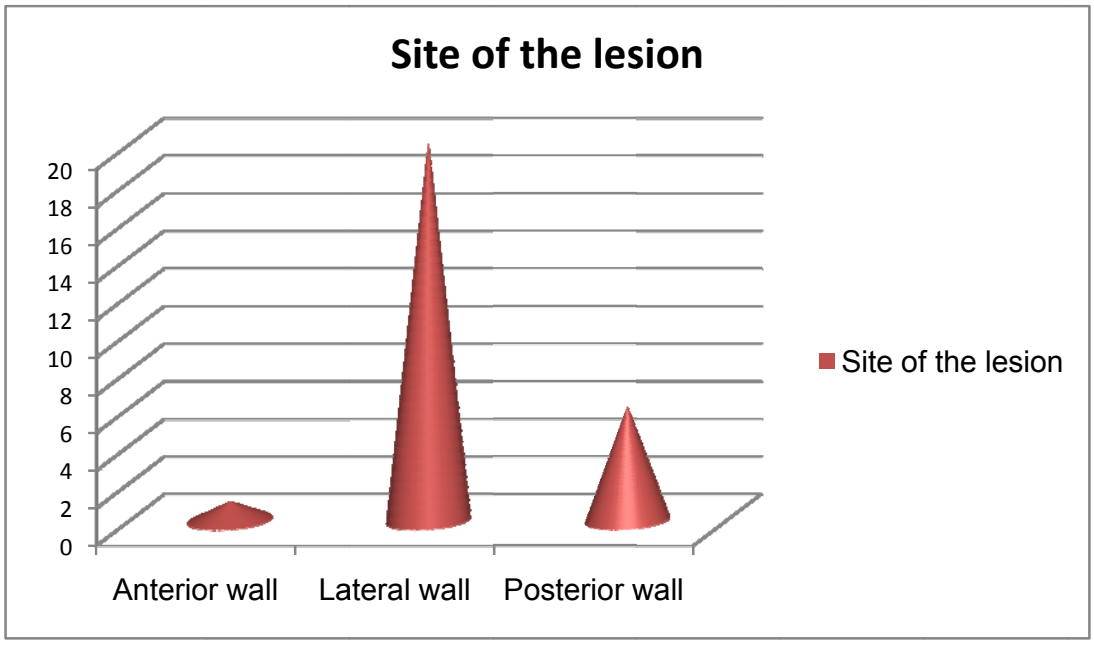

Figure 4: Site of the lesion

Out of these 27 patients, 24 had intravesical mitomycin instilled. It's a protocol that 40mg of mitomycin diluted in 40ml of saline is instilled after the primary resection if it is not contraindicated. Three patients after the primary resection were thought to be muscle invasive; hence no instillation was carried out. At the completion of the primary resections, all of them had the base of the lesion resected separately, and sent for histopathology. All the histopathological specimens had the deep muscle (detrusor) identified and was not involved with tumor**.**

The second resection is usually planned within a span of 4 to 8 weeks. In the study group, the mean time for the second resection is 6weeks 5 days (3

weeks to 12 weeks). None of the patients had any complaints in the intervening period.

During the second resection, the scar was identified at the previous resected sites. The majority of the scars were healthy. Six patients (22.2%) had a visible lesion seen during the second resection. Five of them were on or around the area of the previous resection. The other one had multiple papillary lesions all over the bladder. Histopathological examination of the second resection revealed tumor in 9 patients (33.3%) (Figure 5)

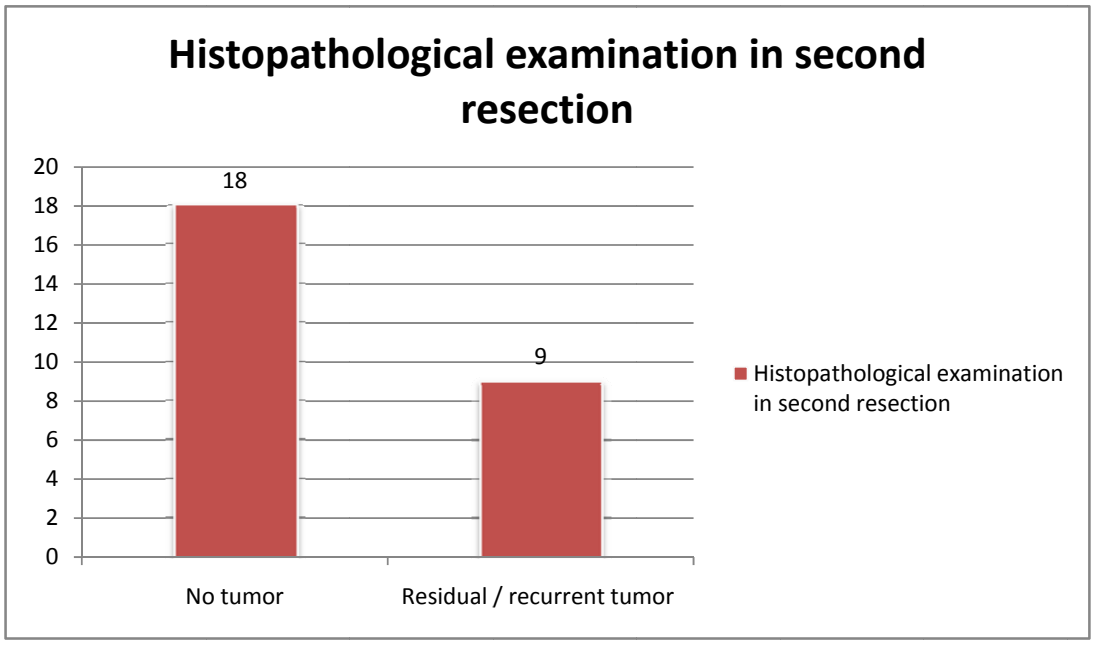

Figure 5: Histopathological examination of the second resection.

There is no strong evidence to classify the tumor in the second resection as residual or recurrent tumor. Among the 9 patients with tumor in the second resection, only one patient (3.7%) had upstaging to muscle invasive disease (Figure 6).

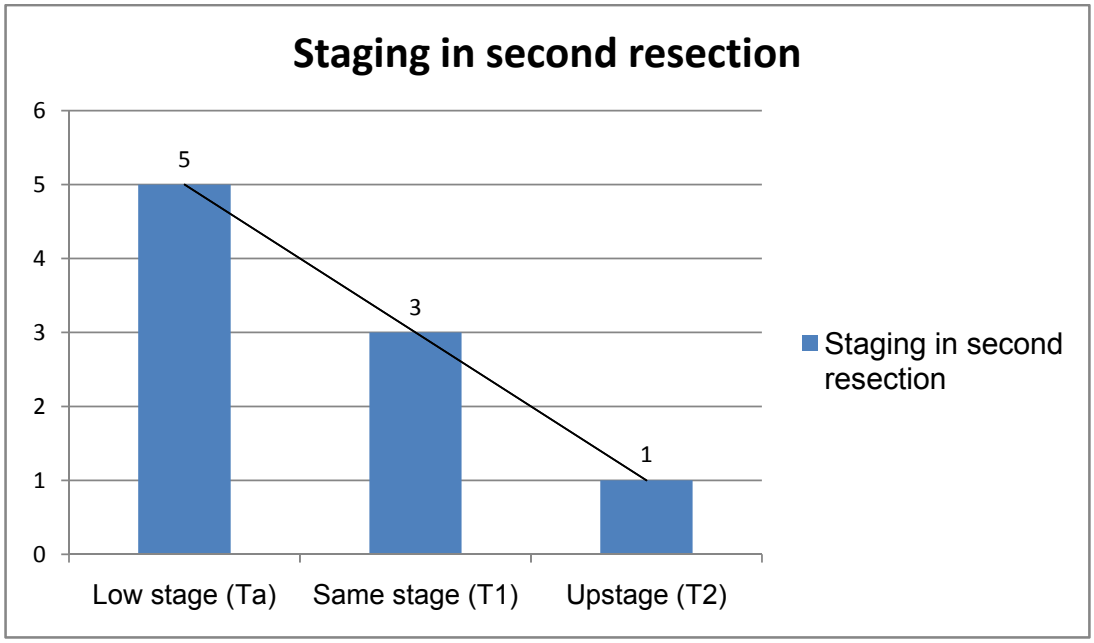

Figure 6: Tumor staging in second resection.

Many variables like the primary characteristics of the lesion, the size of the lesion, muscle in the primary resection specimen and associated CIS assessed and correlated with the result of the second resection. Only 3 patients had a secondary CIS in the primary resected specimen among the study group. On the second resection, two were positive for tumor and one did not have tumor in the second resection. All the primary resections had uninvolved deep muscle in the specimen.

When the primary characteristics of the lesions were considered, more than 85% (13/15) of solitary papillary lesions did not have tumor in the second resection. Five of 9 multiple papillary lesions (71.4%) and 2 of the 3 (66.6%) sessile lesions had tumor in the second resection (Figure 7). There was a significant association between lesion type and positivity (p=0.04). The chances of tumor positivity in the second resection were maximum in sessile tumors followed by the multiple papillary and least in the solitary papillary lesions. The relative risk was 4.17 times more in the multiple papillary group when compared to solitary lesions (RR 4.17, CI-95%, 1.01-17.18). The relative risk was 5 times more in the sessile group when compared with the solitary papillary lesions (RR 5.0, CI-95%, 1.1-22.8). The chances of tumor positivity in the second resection in sessile and multiple papillary groups were high and were statistically significant when compared to solitary papillary lesions.

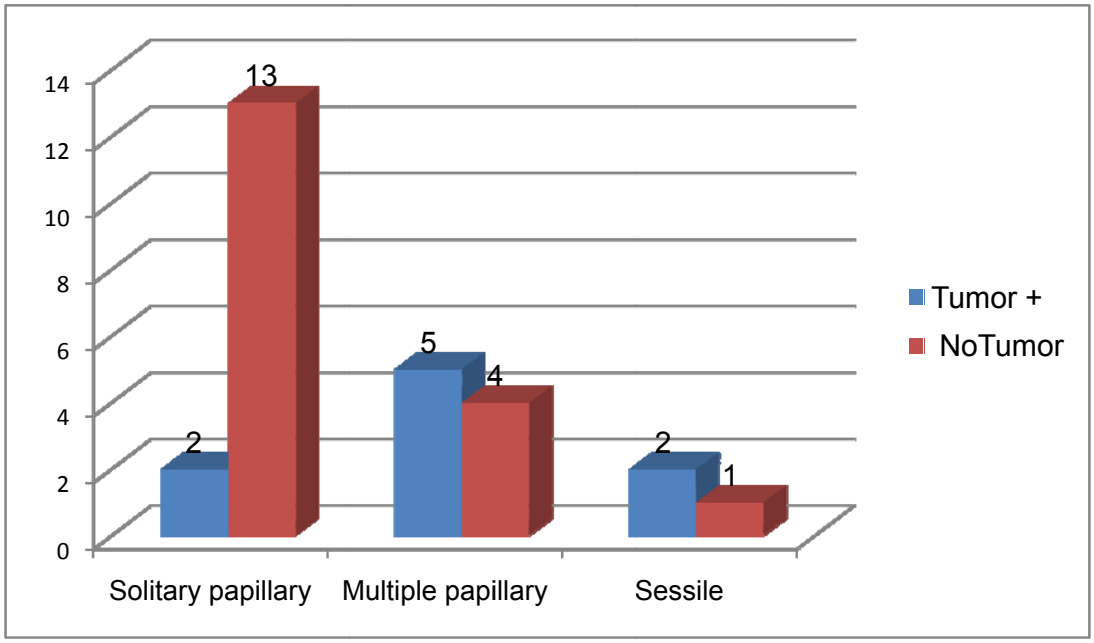

Figure 7: Histopathology in second resection according to lesion characteristics.

Tumor size from the primary resection was analyzed with the positivity of the second resection. There were a total of 12 lesions with more than 3cm in size of which, 8 had tumor positivity in the second resection (66.6%). Only 1 of the 15 lesions (6.6%) of < 3 cm in size had tumor positivity in the second resection (Figure 8). There was a significant association between the size of the lesion and positivity (p=0.001). The chances of tumor positivity in the second resection was high with a lesion of more than 3 cm in size. The relative risk was 10 times more in the tumors with size more than 3cm when compared with the lesions of size <3cm. (RR 10, CI-95%, 1.44-69.3).

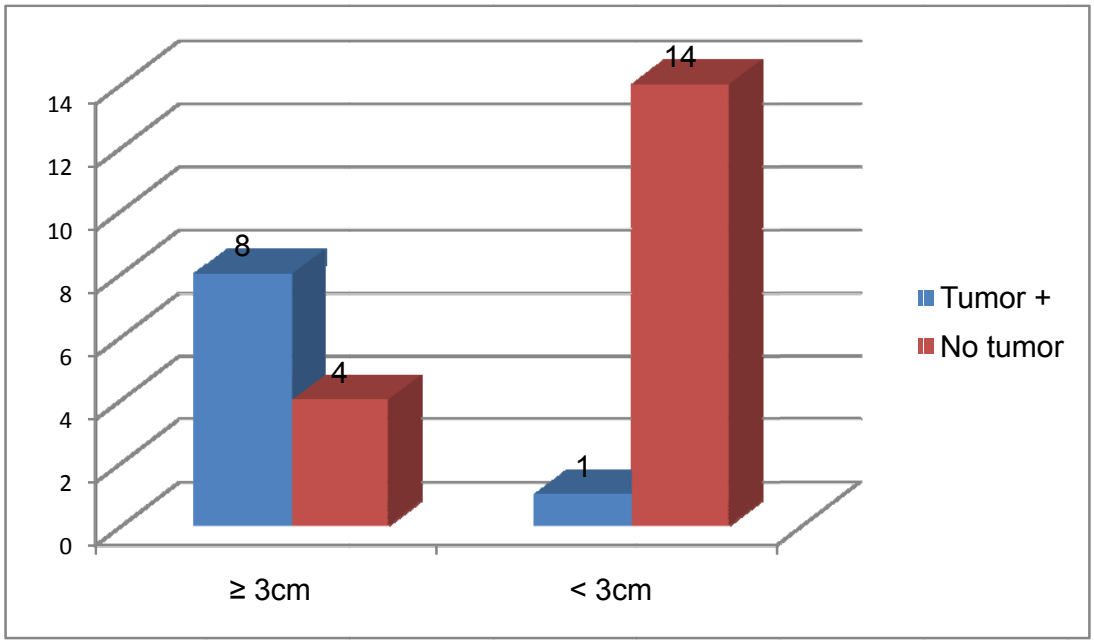

Figure 8: Size of the primary lesion and tumor positivity in second resection.

These two variables i.e. the size of the tumor and the characteristics of the primary lesion together were analyzed with the presence or absence of the tumor in the second resection. Of the 9 patients with tumor positivity in the second resection, 8 had ≥3cm primary lesions, and 4 of them were among the multiple papillary lesion (Figure 9). There were two lesions from the solitary papillary group and 2 from the sessile group who had >3cm lesion who had tumor positivity in the second resection

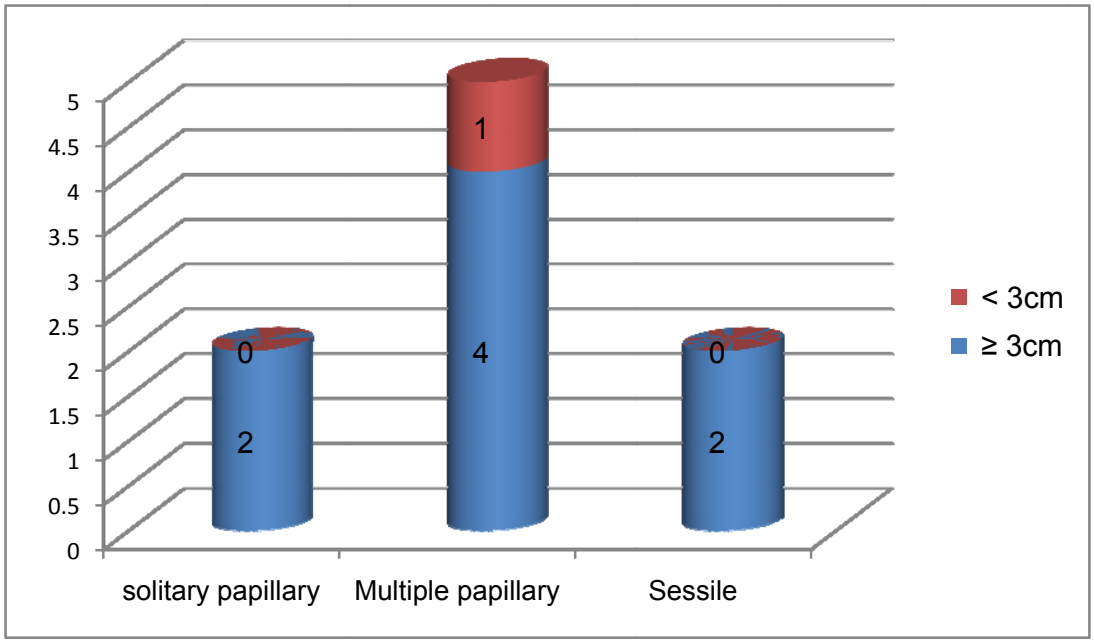

Figure 9: Characteristics and the size of the primary lesion and the tumor positive second resection

Out of the eighteen patients who did not have tumor in the second resection, 13 patients were in solitary papillary group, 4 in the multiple papillary and one in the sessile group. (Figure 10)

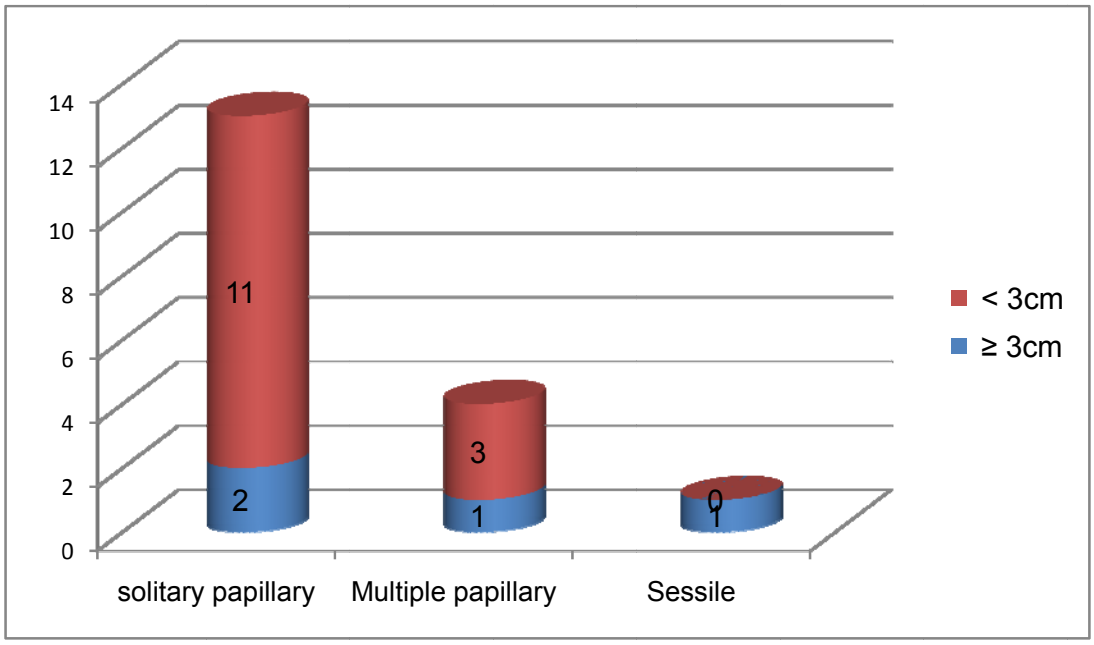

Figure 10: Characteristics & size of the primary lesion and negative second resection

In the study group, of the 27 patients who had second resection, 15 had solitary papillary lesions. Eleven of them were of <3cm in size and none of them had tumor in the second resection. Four had >3cm lesion of which 2 had tumor in the second resection (Figure 11). Of the 9 patients with multiple papillary primary lesions, 5 had lesions >3cm in size and 4 of which had tumor in the second resection. The remaining 4 patients with <3cm size primary lesions, only one had a tumor in the second resection (Figure 12). All the 3 sessile lesions were >3cm in size and two of them had tumor in the second resection.

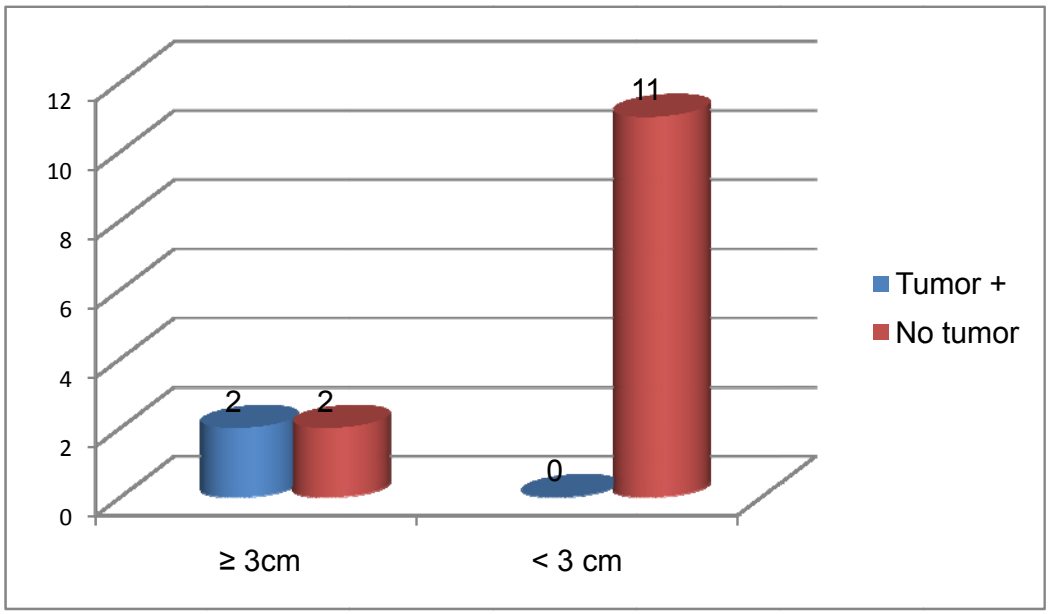

Figure 11: Solitary papillary lesions, primary lesion size and positive second resection

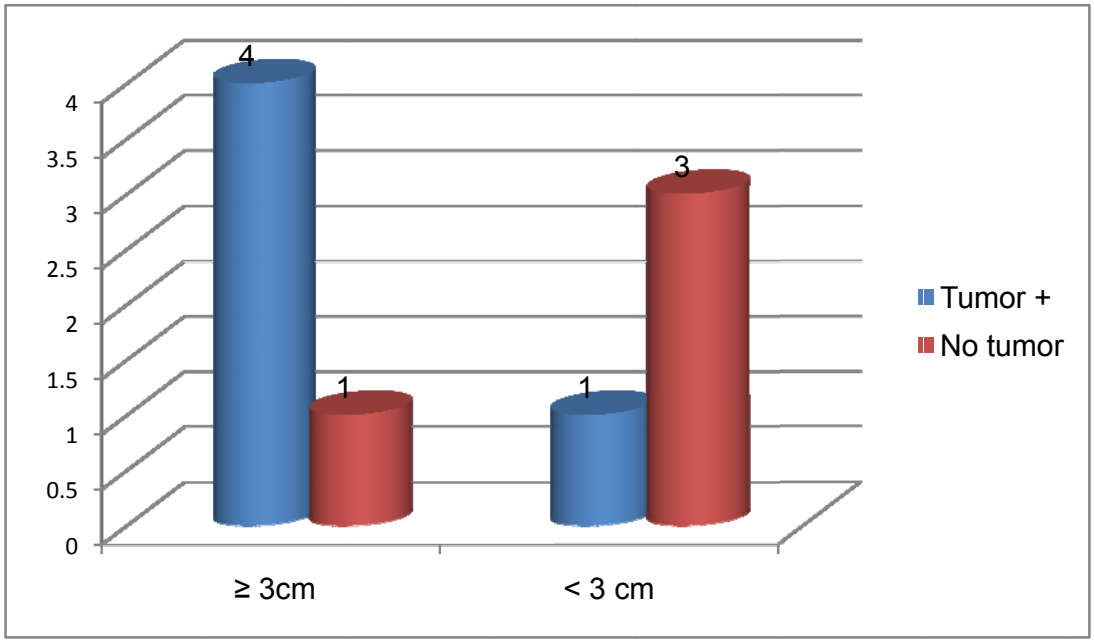

Figure 12: Multiple papillary lesions, primary lesion size and positive second resection

Out of the 9 (33.3%) patients with positive second resection, 5 (18.5%) had low stage disease. Two were solitary papillary and two were multiple papillary lesions and one was a sessile lesion. Four of them had lesions <3cm in size. Three patients (11.1%) had the same stage (T1G3) and 1 patient (3.7%) had upstaging to T2 disease. Same or higher stage disease in the second TUR is seen in multiple papillary (3 patients) and sessile lesion (one patient).

DISCUSSION

DISCUSSION

Bladder cancer is known to occur in the elderly age group, and mostly in the 6th and 7th decade of life. In our study, most of the patients were in the fifth and sixth decade. Eventhough smoking is attributed as a risk factor which significantly increases the risk of bladder cancer, nearly half the patients with TCC in our study were nonsmokers.

TURBT is the initial step in the management of bladder cancer. A technically complete primary resection is warranted for accurate pathological staging and grading of the tumor. After complete resection of all the visible tumors, deep muscle is resected separately for histopathology. If the resected specimen has no muscle, there is a potential for understaging T1 tumors. The important factor is the complete primary resection of the bladder tumor. Presence of the uninvolved muscularis propria in the resected specimen is the only identification for a complete resection [77]. Retrospective studies have shown that residual disease can be seen in upto 68% cases [78]. These high rates may also have been due to the fact that no muscle was present in many of the primary TUR specimens. Forty nine percent of T1 lesions without muscle in the resected specimen were understaged when compared to only 14% with muscle in the resected specimen [30]. Understaging was reported in 64% of T1 tumors when muscle was absent in the specimen versus 30% when it was present [57]. All our resections had muscularis propria sampled at the end of the resection and separately sent for HPE which were tumor free. This can explain why only 3.7% of our patients were upstaged at the second resection.

Tumor architecture, papillary or sessile, and multifocality of these lesions, and the size of the lesion are important prognostic factors for recurrence and progression of the disease. A solitary papillary lesion is considered to be a good prognostic factor as against multiple papillary and sessile lesions [73]. In our series, among the 15 patients with solitary papillary lesions, two had tumor positive in the second resection and both of them were >3cm lesions. All the 11 solitary papillary lesions which were <3cm were tumor free in the second resection and 2 of the >3cm lesions were also free of tumor in the second resection. Perhaps this is the subgroup, solitary papillary with <3cm in size lesions, that are least likely to benefit from a second resection. Multiple papillary lesions and the sessile lesions had significant positivity in the second resection. More than fifty percent of the multiple papillary lesions and 66.6% of the sessile lesions had tumor positivity in the second resection. The relative risk is 4.17 times more in the multiple papillary group when compared to solitary lesions (RR 4.17, CI-95%, 1.01-17.18). The relative risk is 5 times more in the sessile group when compared with the solitary papillary lesions (RR 5.0, CI-95%, 1.1-22.8). The chances of tumor positivity in the second resection in sessile and multiple papillary groups are high and are statistically significant when compared to solitary papillary lesions. The patient who had upstaging of the disease had primary multiple papillary lesions which was >3cm in size.

The size of the primary lesion is also a useful prognosticating factor in these lesions. Many studies have proved a lesion <3cm will have decreased chances of recurrence and progression and this in included in the EAU guidelines of non muscle invasive bladder tumor. In our study, out of 15 patients with a <3cm primary lesion, 14 (93.3%) of them did not have a tumor in second

resection. The chances of tumor positivity in the second resection are high with a lesion of more than 3 cm in size. The relative risk is 10 times more in the tumors with size more than 3cm when compared with the lesions of size <3cm. (RR 10, CI-95%, 1.44-69.3). The one which had a tumor in the second resection is a multiple papillary lesion which itself carries a poor prognosis even if size is not considered.

Considering these two good prognostic factors, i.e size <3cm, and the solitary papillary primary lesion, a select group of patients did not benefit much from the second resection. In this study, all the patients with primary solitary papillary lesion of <3cm size were free of tumor in the second resection. Another factor is the invasion of lamina propria superficial to the muscularis mucosa (T1a) which is considered a good prognostic factor as against the lamina propria deeper to muscularis mucosa [75]. Questions have been raised whether a second resection is really necessary in a well performed initial resection of high grade T1 solitary papillary lesions of <3cm in size with only superficial invasion of lamina propria (T1a) with negative deep muscle biopsy especially when intravesical BCG is planned [76,77].

A comparison of similar studies is shown in table 5. Emphasis was not given to complete primary resection with curative intent in many of them. One series had muscle in only 63% of the primary TURBT specimens [30]. In another, though the presence of muscularis propria was not mentioned in the primary TURBT and 72% of the solitary lesions were tumor free at re-resection [24]. None had muscle in the resected specimen in another series, where 42 T1G3 patients

underwent primary TURBT [23]. The primary characteristic of the lesion which is an important prognostic factor was also not considered in many of these studies.

Table 5: Comparisons of the similar studies

Study	n	PRIMARY LESION			MUSCLE IN HPE	HPE OF SECOND TUR				
		Solitary	Multiple	Sessile	Primary TURBT	No Tumor	Same tumor	Lower tumor	CIS	Up Stage
Dalbagni et al 2002	15	NS	9	NS	6 (40)	1	13	0	1	0
Schips et al	52	25	14	13	NS	29	9	5	0	9
Herr et al 1999	58	NS	NS	NS	35(63)	13	14	15	0	16
Dalbagni et al 2009 [79]	523	NS	NS	NS	242(42)	NS	NS	NS	NS	NS
Our study	27	15	09	03	27(100)	18	03	05	00	01

n = number of patients

Percentage in parentheses

NS = not specified

CONCLUSION

CONCLUSION

There is a need to improve the risk stratification to optimize the treatment of high grade T1 ladder cancer. With the available scientific data, a second resection is recommended in all patients with high grade T1 urothelial bladder carcinoma and it does identify residual disease and invasive disease. Patients with T1G3 tumors do not represent a homogenous group. Isolated solitary papillary lesions may be the only group where the need for the second TUR can be avoided. The dilemma is whether a second TUR is really necessary in a well performed initial resection of high grade T1 solitary small papillary lesion, with only superficial invasion of lamina propria (T1a). In our study, among the patients with solitary papillary lesion and size <3cm, none had tumor in the second TUR and therefore did not require a second TUR. A well designed multicentric prospective study with a large cohort assessing various risk factors of high grade T1 lesions is necessary to determine the subgroups, if any, where a second TUR can be avoided.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Murta-Nascimento C, Schmitz-Dra¨ger BJ, Zeegers MP, et al. Epidemiology of urinary bladder cancer: from tumour development to patient's death. World J Urol 2007;25:285–95.
2. Colombel M, Soloway M, Akaza H et al. Epidemiology, Staging, Grading, and Risk Stratification of Bladder Cancer. Eur urol. 2008;Sup 7:618-26.
3. American Cancer Society. Cancer facts and figures 2006. Atlanta, Georgia: American Cancer Society; 2006.
4. Ferlay J, Autier P, Boniol M et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007;18:581-92.
5. McCahy PJ, Harris CA, Neal E. The accuracy of recording of occupational history in patients with bladder cancer. Br J Urol 1997;79:91–93.
6. Zeegers MP, Tan FE, Dorant E et al. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer 2000;89:630–39.
7. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005;66:4–34.
8. IARC (2004). Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum, 83,1-1438.
9. Vineis P & Simonato L. Proportion of lung and bladder cancer inmales resulting from occupation: a systematic approach. Arch Environ Health, 1991;46:6-15.
10. Chapter 75–76. In.. Walsh PC, Retik AB, Vaughan ED, Wein AJ, Editors. Campbell's Urology. 9th edition. Pennsylyania.. 2007.

11. .Kantor AF, Hartge P, Hoover RN et al. Epidemiological charecteristics of squamous cell carcinoma and adenocarcinoma of the bladder. Cancer Res, 1988;48:3853-55.

12. Aben KKH, Witjes JA, Schoenberg MP et al. Familial aggregation of urothelial cell carcinoma. Int J Cancer 2002;98:274–78.

13. . Sauter G, Algaba F, Amin M, et al. Tumours of the urinary system: non-invasive urothelial neoplasias. In: Eble JN, Sauter G, Epstein JI, Sesterhenn I, editors.WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon: IARCC Press; 2004.

14. Babjuk M, Oosterlinck W, Sylvester R et al. EAU guidelines on non Muscle Invasive Urothelial Carcinoma of the Bladder. Euro Urol. 2008;54:303-14.

15. Soloway MS, Lee CT, Steinberg GD et al. Difficult decisions in urologic oncology: Management of high-grade T1 transitional cell carcinoma of the bladder. Urol Oncol. 2007;25:338-40.

16. Masood S, Sriprasad S, Palmer JH et al. T1G3 bladder cancer - Indications for early cystectomy. Int Urol Nephrol. 2004;36:41-44.

17. Herr HW, Donat SM, Dalbagni G. Can restaging transurethral resection of T1 bladder cancer select patients for immediate cystectomy. J Urol. 2007;177:75-79.

18. Herr HW, Donat SM. A re-staging transurethral resection predicts early progression of superficial bladder cancer. BJU Int. 2006;97:1194-98.

19. Nieder AM, Brausi M, LammD et al.. Management of stage T1 tumors of the bladder: International Consensus Panel. Urology 2005;66:108-25.

20. Borkowski A. Superficial bladder cancer T1G3: the choice of treatment. BJU Int. 2002;89:623-7.

21. Herr HW, Reuter VE. Progression of T1 bladder tumors: better staging or better biology? Cancer. 1999;86:908-12.

22. Peyromaure M, Zerbib M. T1G3 transitional cell carcinoma of the bladder: recurrence, progression and survival. BJU Int. 2004;93:60-63.

23. Brauers A, Buettner R, Jakse G. Second resection and prognosis of primary high risk superficial bladder cancer: Is cystectomy often too early? J Urol. 2001;165:808-10

24. Schips L, Augustin H, Ziqeuner RE et al. Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? Urology 2002;59:220-23.

25. Cookson MS, Herr HW, Zhang ZF et al. The treated natural history of high risk superficial bladder cancer: 15-year outcome. J Urol 1997;158:62–67.

26. Serretta V. T1HG bladder tumours: so many papers, do we need them? Yes, we do! Eur Urol. 2009;56:911-3.

27. Kulkarni GS, Hakenberg OW, Gschwend JE et al. An updated critical analysis of the treatment strategy for newly diagnosed high-grade T1 (previously T1G3) bladder cancer. Eur Urol. 2010;57:60-70.

28. Smith PH, Hall RR. Prognostic factors, treatment options and follow-up of Ta and T1 bladder tumours. In Hall RR, editor. The Clinical Management of Bladder Cancer. London: Arnold; 1997.p. 97–118.

29. Improving Outcomes in Urological Cancers. The Manual. Guidance on Cancer Services. London: National Institute for Clinical Excellence; 2002.

30. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. J Urol 1999;162:74–76.
31. Richards B, Parmar MK, Anderson CK et al. Interpretation of biopsies of ‘‘normal’’ urothelium in patients with superficial bladder cancer. MRC Superficial Bladder Cancer Sub Group. Br J Urol 1991;67:369–75.
32. Witjes JA, Kiemeney LA, Schaafsma HE et al. The influence of review pathology on study outcome of a randomized multicentre superficial bladder cancer trial. Members of the Dutch South East Cooperative Urological Group. Br J Urol 1994;73:172–76.
33. Oosterlinck W, Lobel B, Jakse G et al. Guidelines on Bladder Cancer. Arnhem: European Association of Urology; 2003.
34. Smith Jr JA, Labasky RF, Cockett AT et al. Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. J Urol 1999;162:1697–701.
35. Heney NM, Ahmed S, Flanagan MJ et al. Superficial bladder cancer: progression and recurrence. J Urol 1983;130:1083–86.
36. Shahin O, Thalmann GN, Rentsch C et al. A retrospective analysis of 153 patients treated with or without intravesical bacillus Calmette-Guerin for primary stage T1 grade 3 bladder cancer: recurrence. J Urol 2003;169:96–100.
37. Griffiths TR, Charlton M, Neal DE et al.Treatment of carcinoma in situ with intravesical bacillus Calmette-Guerin without maintenance. J Urol 2002;167:2408–12.

38. William Turner. T1G3 Bladder Tumours: The Case for Conservative Treatment. Eur Urol 2004;45:401–05.
39. Soloway M, Lee C, Steinberg G et al. Difficult decisions in urologic oncology: Management of high-grade T1transitional cell carcinoma of the bladder. Urologic Oncology: Seminars and Original Investigations 2007;25:338–340.
40. Oosterlinck W. The management of superficial bladder cancer. BJU Int 2001;87: 135–41.
41. Borkowski A. Superficial bladder cancer T1G3: the choice of treatment. Br J Urol Int 2002;89:623–627.
42. Thalmann G. Organ Preservation for T1G3 Bladder Cancer:Is It Feasible? Eur Urol 2008;53:27–29.
43. Herr H. Tumor progression and survival of patients with high grade, noninvasive papillary (TaG3) bladder tumours:15-years outcome. J Urol 2000;163:60–62.
44. Lebret T, Bohin D, Kassardjian Z et al. Recurrence, progression and success in stage Ta grade 3 bladder tumours treated with low dose BCG. J Urol 2000;163: 63–67.
45. Medical Research Council Working Party on Urological Cancer Subgroup on Superficial Bladder Cancer. The effect on intravesical thiotepa on tumour recurrence after endoscopic treatment of newly diagnosed superficial bladder cancer. A further report with long-term follow-up of a Medical Research Council randomized trial. Br J Urol 1994; 73: 632–38.
46. Herr HW, Reuter VE. Progression of T1 bladder tumors. Cancer 1999; 86:908–9.

47. Stockle M, Alken P, Engelmann G et al. Radikale Zystektomie- Oft zu spat? Akt Urol 1986;17:234–39.(Article in German – Abstract Translate).
48. Dutta SC, Shappell SB, Smith JA et al. Radical cystectomy in high-risk nonmuscle-invasive transitional cell carcinoma: indications and outcomes. J Urol 2000;163 (Suppl.):148,A662.
49. Sylvester RJ, van der Meijden AP, Oosterlinck W et al. Predicting recurrence and progression in individual patients with stage TaT1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–77.
50. Loening S, Fallon B, Narayana A et al. Urinary cytology and bladder biopsy in patients with bladder cancer. Urology 1978;11:591-95.
51. Fujimoto N, Haradas S, Terado M, et al. Multiple biopsies of normal looking urothelium in patients with superficial bladder cancer: are they necessary? Int J Urol 10: 631– 635, 2003.
52. van der Meijden AP, Oostelinck W, Brausi M, et al. Significance of bladder biopsies in Ta-T1 bladder tumors: a report from EORTC GU Group. Eur Urol 1999;35:267–271.
53. May F, Treiber V, Hartung R, et al. Significance of random bladder biopsies in superficial bladder cancer. Eur Urol 2003;44:47–50.
54. Tolley DA, Parmar MK, Grigor KM, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. J Urol 1996;155:1233–38.
55. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence

in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90.

56. Jakse G, Algaba F, Malmstro P et al. A Second-Look TUR inT1 Transitional Cell Carcinoma: Why? Eur Urol 2004;45:539–46.
57. Dutta SC, Smith JA Jr, Shappell SB, et al. Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. J Urol 2001;166:490–93.
58. Divrik RT, Sahin AF, Yildirim U et al. Impact of routine second transurethral resection on the long-term outcome of patients with newly diagnosed pT1 urothelial carcinoma with respect to recurrence, progression rate, and disease-specific survival: a prospective randomised clinical trial. Eur Urol. 2010;58:185-90.
59. Zurkirchen MA, Sulser T, Gaspert A, et al. Second transurethral resection of superficial transitional cell carcinoma of the bladder: a must even for experienced urologists. Urol Int 2004;72:99–102.
60. Grimm MO, Steinhoff C, Simon X, et al. Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. J Urol 2003;170: 433–37.
61. Pawinski A, Sylvester R, Kurth KH, et al. A combined analysis of European Organization for Research and Treatment of Cancer, and Medical Research Council randomized clinical trials for the prophylactic treatment of Ta T1 bladder cancer. European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council Working Part on Superficial Bladder Cancer. J Urol 1996;156:934–41.

62. Huncharek M, McGarry R, Kupelnick B. Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res 2001;21:765–70.
63. Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non–muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. Eur Urol 2008;53:709–19.
64. Shelley MD, Court JB, Kynaston H et al. Intravesical bacillus Calmette-Guerin in Ta and T1 bladder cancer.Cochrane Database Syst Rev 2000:CD001986.
65. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964–70.
66. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal metaanalysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90–95.
67. Cheng CW, Ng MT, Chan SY et al. Low dose BCG as adjuvant therapy for superficial bladder cancer and literature review. ANZ J Surg 2004;74:569–72.
68. Hurle R, Losa A, Ranieri A et al. Low dose Pasteur bacillus Calmette-Guerin regimen in stage T1, grade 3 bladder cancer therapy. J Urol 1996;156:1602–05.

69. Martinez-Pineiro JA, Flores N, Isorna S, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guerin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int 2002;89:671–80.

70. Yoneyama T, Ohyama C, Imai A, et al. Low-dose instillation therapy with bacille Calmette-Guerin Tokyo 172 strain after transurethral resection: historical cohort study. Urology 2008;71:1161–65.

71. Weiss C, Wolze C, Engehausen DG, et al. Radiochemotherapy after transurethral resection for high-risk T1 bladder cancer: an alternative to intravesical therapy or early cystectomy? J Clin Oncol 2006;24:2318–24.

72. Harland SJ, Kynaston H, Grigor K, et al. A randomized trial of radical radiotherapy for the management of pT1G3 NXM0 transitional cell carcinoma of the bladder. J Urol 2007;178:807–13.

73. Serretta V, Ruggirello A, Dispensa N et al. Multiplicity and history have a detrimental effect on survival of patients with T1G3 bladder tumors selected for conservative treatment. J Urol. 2008;180:886-90.

74. Editorial in Herr HW, Donat SM, Dalbagni G. Can restaging transurethral resection of T1 bladder cancer select patients for immediate cystectomy. J Urol. 2007; 177:75-79.

75. Orsola A, Trias I, Ravento´s CX et al. Initial high-grade T1 urothelial cell carcinoma: feasibility and prognostic significance of lamina propria invasion microstaging (T1a/b/c) in BCG-treated and BCG-non-treated patients. Eur Urol 2005; 48:231–8, discussion 238.

76. Orsola A, Cecchini L, Morote J . Re: Marko Babjuk, Willem Oosterlinck, Richard Sylvester, et al. EAU guidelines on non-muscle-invasive urothelial

carcinoma of the bladder. Eur Urol 2008;54:303-14.Eur Urol. 2009;55:e15-16.

77. Babjuk M. Second resection for non-muscle-invasive bladder carcinoma: current role and future perspectives. Eur Urol 2010;58:191–92.
78. Orsola A, Cecchini L, Raventos CX, Trilla E, Planas J, Landolfi S et al. Risk factors for positive findings in patients with high grade T1 bladder cancer treated with transurethral resection of bladder tumor (TUR) and bacilli Calmette-Guerin therapy and the decision for a repeat TUR. BJU Int.2010;105:202-07.
79. Dalbagni G, Vora K, Kaag M, Cronin A, Bochner B, Donat SM et al. Clinical Outcome in a Contemporary Series of Restaged Patients with Clinical T1 Bladder Cancer. Eur Urol.2009;56:903-910.

ANNEXURE

Annexure 1	Informed Consent
Annexure 2	Porforma
Annexure 3	Master Charts

INFORMED CONSENT

Study Title:

To assess the role of second resection of T1G3 bladder tumors.

A. CONSENT FOR PROCEDURE

1. I _____ authorize the performance of Transurethral resection of bladder tumor (TURBT) and second TURBT if needed.

2. I understand my diagnosis / condition to be: BLADDER TUMOR.

3. I have been told about the surgery (which includes information about the complications), the histopathological examination of the resected tissue, and the management plan to be decided after the final biopsy report

4. I know that the management of the disease varies with the extent of the disease spread (Biopsy report).

5. I have been told about and understand the risks and benefits of the procedure. I understand that there are risks like pain, urinary tract infection, stricture urethra, residual and recurrence of disease, perforation of the urinary bladder, and the further management plan according to the extent of the disease spread, and in very very rare instance death.

6. I understand that photographs and/or video or electronic recordings may occur or data collected during my procedure may be used for internal performance improvement or educational / publication purposes.

B. CONSENT FOR ANESTHESIA OR SEDATION

I consent to the administration of anesthesia medication by or under the direction of the doctor. I acknowledge that I have been informed about nature of the planned anesthesia and that I understand the risks of anesthesia to include: head ache, back ache, temporary loss of sensory and motor function of the lower extremities, allergic reactions to medications, changes in breathing. changes a blood pressure and heart function, nausea and vomiting, aspiration of stomach contents and/or excitement. I understand that recall of the procedure is possible.

C. PATIENT OR LEGAL REPRESENTATIVE SIGNATURE

By signing below I state that I am 18 years of age or older, or otherwise authorized to consent. I have read or have had explained to me the contents of this form. I have had a chance to ask questions and all of my questions have been answered.

_____ _____

Signature of Patient or Legal Representative Name
Date

_____
Relationship in case of Guardian / Legal Representative

D. PHYSICIAN STATEMENT

I have explained the procedure, including the possible risks, complications, and anticipated risks to the patient and/or his/her representative. The patient and/or their representative has communicated to me that they understand the contents of this form.

_____

Name and Signature of the doctor. Date.

_____

Name and Signature of Witness Date

TCC URINARY BLADDER PROFORMA

Name: H No: URO1 / URO2

Age: Yrs Sex: M / F Phone Numbers

Chief Complaints: X months

O / E: Bladder bimanually palpable - Y / N.

Creatinine: mg%. Cytology:

Radiology: USG:

IVU:

CECT:

Radiology Staging:

Past History:

Previous biopsy: Procedure Details

Date

Bx Report

Slide review

Procedure: TURBT / Cold cup biopsy / Re TURT (for recurrence)

Date: **Surgeon**: **Assesment:**

No. of lesions: 1 / 2 / 3 / 4 / 5 / 6 / Multiple

Site / Size : Bladder neck / Dome

Posterior wall / Anterior wall

Left lat wall / Right lat wall

Distance from orifice:

Assosiated lesions:

Appearance: Invasive / Non invasive **Bimanually Palpable** : Y / N

Mitomycin 40mg: Y / N

Complications:

Biopsy: CIS / Ta / T1 / T2 / T3 / T4

PUNLMP / Low Grade / High Grade

G1 / G2 / G3

Muscle in specimen:

Options: Survelliance BCG Re stage TURBT

Radical Cystectomy with Ileal Conduit

Radical Cystectomy with Orthotopic Bladder

Radiotherapy / Chemotherapy

Name:
Hospital No.

Re TURBT for STAGING

Procedure: Re TURT (for staging)

Date: **Surgeon**:

Previous scars: **Recurrence:** Y / N

No. of lesions: 1 / 2 / 3 / 4 / 5 / 6 / Multiple

Site / Size: Bladder neck / Dome

Posterior wall / Anterior wall

Left lat wall / Right lat wall

Re resection from:

Distance from orifice:

Associated lesions:

Appearance: Invasive / Non invasive

Bimanually: Palpable / Not palpable

Mitomycin 40mg: Y / N

Complications:

Biopsy: No tumor Same stage/grade Up stage Down stage

Previous: CIS / Ta / T1 / T2 / T3 / T4 PUNLMP / Lw Grde / Hgh Grde

Now : : CIS / Ta / T1 / T2 / T3 / T4 PUNLMP / Lw Grde / Hgh Grde

sno.	Name:	H No:	Stage	CIS	Unit	Age:	Sex	Complaints	GROSS	TOTAL	PAINLESS	CLOTS	sno.	Dur_comp (months)	Comorb	sno.
1	Amar Ghosh	449729d	1G3	no	1	54	Male	Haematuria	yes	yes	yes	yes	1	1	nil	1
2	Raman	492917d	1G3	no	1	65	Male	Haematuria	yes	yes	yes	no	2	4	HT	2
3	Sisir	527627d	1G3	no	1	55	Male	Haematuria	yes	yes	yes	no	3	2	nil	3
4	Parhta sen	6387934d	1G3	no	1	41	Male	Haematuria	yes	yes	yes	yes	4	24	nil	4
5	Dasarath	418178d	1G3	no	2	71	Male	Haematuria	yes	yes	yes	no	5	3	nil	5
6	Ahindra	471741d	1G3	no	2	63	Male	Haematuria	yes	yes	yes	yes	6	4	nil	6
7	Polu yesoda	500284d	1G3	CIS	2	55	Female	Haematuria	yes	yes	yes	yes	7	8	nil	7
8	Safidul	590528d	1G3	no	2	45	Male	Haematuria	yes	yes	yes	no	8	60	DM	8
9	Meena	809022d	1G3	no	2	60	Female	Haematuria	yes	yes	yes	no	9	6	DM	9
10	Manikkam	447798d	1G3	no	1	39	Male	Haematuria	yes	yes	yes	yes	10	12	nil	10
11	Godudhar	430124d	1G3	no	1	56	Male	Haematuria	yes	yes	yes	yes	11	6	nil	11
12	Lakshmi	494365c	1G3	no	1	56	Female	Haematuria	yes	yes	yes	yes	12	1	HT	12
13	Chandrakala	870276c	1G3	no	1	63	Female	Haematuria	yes	yes	yes	yes	13	1	nil	13
14	Bishnupada	649841d	1G3	no	1	70	Male	Haematuria	yes	yes	yes	yes	14	1	nil	14
15	Ashok	271382d	1G3	no	1	49	Male	Haematuria	yes	yes	yes	no	15	1	HT	15
16	Subramanyam	690289d	1G3	no	1	48	Male	Haematuria	yes	yes	yes	yes	16	3	nil	16
17	Saroj Kumar	750916d	1G3	no	1	48	Male	Haematuria	yes	yes	yes	no	17	2	nil	17
18	Basudev	755613d	1G3	no	1	52	Male	Haematuria	yes	yes	yes	yes	18	240	nil	18
19	Jasintha	463166d	1G3	no	2	50	Female	Haematuria	yes	yes	yes	no	19	12	nil	19
20	Ismail	653399d	1G3	no	2	64	Male	Haematuria	yes	yes	yes	yes	20	1	DM, HT	20
21	Khudi ram	665695d	1G3	no	2	61	Male	Haematuria	yes	yes	yes	no	21	3	nil	21
22	Alimuddin	740447c	1G3	no	2	75	Male	Haematuria	yes	yes	yes	no	22	2	DM, HT	22
23	Rabindranath	685474d	1G3	no	2	67	Male	Haematuria	yes	yes	yes	yes	23	12	HT, DM	23
24	Dhanpal	681866d	1G3	no	2	72	Male	Haematuria	yes	yes	yes	yes	24	2	nil	24
25	Anderson	814437d	1G3	CIS	1	37	Male	intermitency	no	no	no	no	25	1	nil	25
26	Balasundaram	938834b	1G3	no	1	49	Male	Haematuria	yes	yes	yes	yes	26	4	HT, DM	26
27	Sateesh	816457d	1G3	no	2	52	Male	Haematuria	yes	yes	yes	no	27	1	nil	27

O/E:Blder bimanly palpable -	Creatinine:	Cytology:	USG:	IVU	CT Scan	Radiology Staging:	Addictions	No / day	sno.
Not palpable	1.1	NS	rt lat wall SOL	filling defect bladder	NA	Non invasive	Smoking	5 to 6	1
Not palpable	1	NS	outside - SOL bldr	NA	NA	Non invasive	Smoking	5 to 6	2
Not palpable	0.9	NS	sol bladder	NA	NA	Non invasive	Smoking	5 t0 8	3
Not palpable	0.9	NS	sol bladder	NA	NA	Non invasive	Smoking	8 to 10	4
palpable	1.6	NS	sol bladder	NA	thick rt vuj	invasive	No	NA	5
Not palpable	1	NS	outside - SOL bldr	NA	NA	Non invasive	Smoking	8 to 10	6
Not palpable	1.1	NS	NA	NA	thick lateral wall	Non invasive	No	NA	7
Not palpable	1	NS	outside - SOL bldr	NA	NA	Non invasive	No	NA	8
Not palpable	1	normal	sol bladder	NA	NA	Non invasive	No	NA	9
Not palpable	0.9	NS	own- sol lt lat wl	,normal	NA	Non invasive	No	NA	10
Not palpable	1.2	NS	post wl SOL	NA	NA	Non invasive	Smoking	five to six	11
Not palpable	0.9	NS	rt lat wall SOL	NA	NA	Non invasive	No	NA	12
Not palpable	0.9	NS	outside - SOL bldr	NA	NA	Non invasive	No	NA	13
Not palpable	1.4	NS	NA	filling defect bladder	NA	Non invasive	Smoking	25 to 30	14
Not palpable	1.1	NS	outside - SOL bldr	NA	NA	Non invasive	No	NA	15
Not palpable	1.1	NS	own- sol lt lat wl	filling defect bladder	NA	Non invasive	Smoking	7	16
Not palpable	1	NS	sol bladder	NA	NA	Non invasive	No	NA	17
Not palpable	0.9	NS	own- sol lt lat wl	NA	NA	Non invasive	No	NA	18
Not palpable	0.9	NS	sol bladder	NA	NA	Non invasive	No	NA	19
Not palpable	1.2	NS	sol bladder	NA	NA	Non invasive	Smoking	4 to 6	20
Not palpable	1.2	NS	sol bladder	NA	NA	Non invasive	Smoking	6 to 8	21
Not palpable	1.6	NS	sol bladder	filling defect bladder	NA	Non invasive	Smoking	3 to 5	22
Not palpable	2	NS	sol bladder	NA	thick wall post	Non invasive	Smoking	6 to 8	23
Not palpable	1	normal	outside - SOL bldr	NA	sol bladder outside	Non invasive	No	NA	24
Not palpable	1	normal	sol bladder	NA	sol bladder	Non invasive	No	NA	25
Not palpable	1.2	normal	sol bladder	filling defect bladder	NA	Non invasive	Smoking	8 to 10	26
Not palpable	1	normal	sol bladder	NA	NA	Non invasive	No	NA	27

No of yrs	Occupation	Procedure:	Date:	site	character	Bladder neck	Dome	Post Wall	Ant wall	Left lat wall	sno.
15	service	TURBT	5/1/2009	lateral wall	multiple papillary	normal	2x2	1x1	normal	3x3	1
20	service	TURBT	7/14/2009	lateral wall	sessile	normal	normal	normal	normal	normal	2
15	service	TURBT	9/1/2009	post wall	multiple papillary	normal	normal	4x4	normal	field change	3
15	business	TURBT	3/24/2010	lateral wall	multiple papillary	normal	normal	1x1	normal	5x5	4
NA	business	TURBT	4/12/2009	lateral wall	papillary	normal	normal	normal	normal	normal	5
35	coolie	TURBT	6/4/2009	lateral wall	multiple papillary	normal	normal	normal	2x1	normal	6
NA	house wife	TURBT	9/30/2009	lateral wall	multiple papillary	normal	normal	1x1,1x1	normal	2x2,2x2,1x1	7
NA	service	TURBT	12/7/2009	lateral wall	papillary	normal	normal	normal	normal	5x4	8
NA	nil	TURBT	11/25/2010	ant wall	sessile	normal	normal	normal	3x2	normal	9
NA	coolie	TURBT	6/5/2009	lateral wall	papillary	normal	normal	normal	normal	2x2	10
20	service	TURBT	4/24/2009	lateral wall	papillary	normal	normal	normal	normal	normal	11
NA	house wife	TURBT	5/6/2009	lateral wall	multiple papillary	normal	normal	normal	normal	normal	12
NA	house wife	TURBT	6/19/2009	lateral wall	multiple papillary	1x1, .5x.5	normal	normal	normal	normal	13
10	business	TURBT	4/13/2010	lateral wall	papillary	normal	normal	normal	normal	normal	14
NA	business	TURBT	5/14/2010	lateral wall	papillary	normal	normal	normal	normal	normal	15
20	service	TURBT	5/18/2010	lateral wall	papillary	normal	normal	normal	normal	5x5	16
NA	service	TURBT	8/10/2010	lateral wall	papillary	normal	normal	normal	normal	2x2	17
NA	coolie	TURBT	8/20/2010	lateral wall	papillary	normal	normal	normal	normal	2x2	18
NA	service	TURBT	25/5/2009	post wall	papillary	normal	normal	1x2	normal	normal	19
30	retierded	TURBT	3/22/2010	lateral wall	multiple papillary	1x1	2x1 patch	normal	normal	normal	20
20	retierded	TURBT	3/31/2010	post wall	papillary	normal	normal	2x2	normal	normal	21
25	retierded	TURBT	4/12/2010	lateral wall	papillary	normal	normal	normal	normal	normal	22
30	service	TURBT	5/20/2010	post wall	papillary	normal	normal	2x2.5	normal	normal	23
NA	business	TURBT	5/3/2010	post wall	sessile	normal	normal	3x3	normal	normal	24
NA	business	TURBT	10/29/2010	lateral wall	multiple papillary	normal	normal	normal	normal	normal	25
15	service	TURBT	10/29/2010	lateral wall	papillary	normal	normal	normal	normal	normal	26
NA	business	TURBT	11/11/2010	post wall	papillary	normal	normal	2x2	normal	normal	27

Rt lat wall	Prostatic urethra	Distance from orifice:	Assosiated lesions:	Appearance:	Biman palp	Resection	MMC 40	Cxs	sno.
5x4, three small	normal	not involved	three small paipllary adjacent to main lesion	non invasive	not palpable	complete	yes	nil	1
3x3	normal	right orifice involved	none	non invasive	not palpable	complete	no	nil	2
normal	normal	not involved	field change over post & lat	non invasive	not palpable	complete	yes	nil	3
normal	normal	not involved	none	non invasive	not palpable	complete	yes	nil	4
4x3.5	normal	right orifice involved	none	invasive	palpable	complete	no	nil	5
6x5	normal	not involved	multiple paillary	non invasive	not palpable	complete	yes	nil	6
normal	,NA	not involved	none	non invasive	not palpable	complete	yes	nil	7
normal	normal	left orifice involved	none	non invasive	not palpable	complete	yes	nil	8
normal	,NA	not involved	none	non invasive	not palpable	complete	yes	nil	9
normal	normal	left orifice involved	none	non invasive	not palpable	complete	yes	nil	10
2x2	normal	not involved	none	non invasive	not palpable	complete	yes	nil	11
4x4, three small	,NA	not involved	three small paipllary adjacent to main lesion	non invasive	not palpable	complete	yes	nil	12
2x2	,NA	not involved	total 2	non invasive	not palpable	complete	yes	nil	13
2x2	normal	not involved	none	non invasive	not palpable	complete	yes	nil	14
2.5x2	normal	not involved	none	non invasive	not palpable	complete	yes	nil	15
normal	normal	left orifice involved	none	invasive	not palpable	complete	no	nil	16
normal	normal	not involved	none	non invasive	not palpable	complete	yes	nil	17
normal	normal	not involved	none	non invasive	not palpable	complete	yes	nil	18
normal	,NA	not involved	none	non invasive	not palpable	complete	yes	nil	19
2x2	normal	not involved	2x2 erythematous patch	non invasive	not palpable	complete	yes	nil	20
normal	normal	right orifice involved	none	non invasive	not palpable	complete	yes	nil	21
2x2	normal	not involved	none	non invasive	not palpable	complete	yes	nil	22
normal	normal	left orifice involved	none	non invasive	not palpable	complete	yes	nil	23
normal	normal	not involved	none	non invasive	not palpable	complete	yes	nil	24
1x1, 1x1, 1x1	normal	right orifice involved	none	non invasive	not palpable	complete	yes	nil	25
5x5	normal	not involved	none	non invasive	not palpable	complete	yes	nil	26
normal	normal	not involved	none	non invasive	not palpable	complete	yes	nil	27

Bx Stage	Grade	Ass CIS	Muscle in Bx	plan	RE RESECTION	DATE	DIFF IN WEEKS	SURGEON	PREV SCAR	sno.
1	3	no	yes	second rx	done	6/16/2009	6		multiple scars	1
1	3	no	yes	second rx	done	9/9/2009	7		scar + tr frm rt orifice	2
1	3	CIS	yes	second rx	done	12/10/2009	6		scar odema	3
1	3	no	yes	second rx	done	6/8/2010	12		scar	4
1	3	no	yes	second rx	done	4/23/2009	6		scar + 1x1 papillary on rt UO	5
1	3	no	yes	second rx	done	8/24/2009	11		scar & tumor	6
1	3	CIS	yes	second rx	done	5/11/2009	5		scar & tr	7
1	3	no	yes	second rx	done	1/18/2010	6		scar & tr	8
1	3	no	yes	second rx	done	1/24/2011	8		scar	9
1	3	no	yes	second rx	done	6/16/2009	6		odematous scar	10
1	3	no	yes	second rx	done	5/12/2009	3		scar	11
1	3	no	yes	second rx	done	7/10/2009	5		scar	12
1	3	no	yes	second rx	done	8/11/2009	7		scar	13
1	3	no	yes	second rx	done	4/6/2010	7		scar	14
1	3	no	yes	second rx	done	6/16/2010	4		scar	15
1	3	no	yes	second rx	done	2/7/2010	6		scar	16
1	3	no	yes	second rx	done	10/9/2010	4		scar	17
1	3	no	yes	second rx	done	9/22/2010	4		scar	18
1	3	no	yes	second rx	done	7/22/2009	7		scar	19
1	3	CIS	yes	second rx	done	6/17/2010	11	11	erythematous scar	20
1	3	no	yes	second rx	done	5/27/2010	8		scar	21
1	3	no	yes	second rx	done	5/23/2010	5		scar	22
1	3	no	yes	second rx	done	7/13/2010	7		scar	23
1	3	no	yes	second rx	done	6/24/2010	7		scar	24
1	3	CIS	yes	second rx	done	1/14/2011	10		scar	25
1	3	no	yes	second rx	done	1/25/2011	11		scar	26
1	3	no	yes	second rx	done	12/22/2010	6		scar	27

RECURRENCE	No. OF LESIONS	Site	BLDER NK	DOME	ANT WAL	POST WAL	LT LAT	sno.
yes	multiple	PW, rt & lt LW	normal	scar	1x1	1x1, 1x1	1x1	1
yes	1	rt orifice	normal	normal	normal	normal	normal	2
odema	odema	post wall odema	normal	normal	normal	odematous scar	normal	3
nil	nil	lat wall	normal	normal	normal	normal	scar	4
1x1 rt UO	1	rt orifice	normal	normal	normal	normal	normal	5
1x1 & .5x.5 on scar,	3	on scar, rt lateral wall	normal	normal	normal	normal	5x5mm	6
2x2mmon scar, 2x2mm ant wall	2	on scar and ant wall	normal	normal	2x2mm	normal	3x3mm	7
2x2cm scar & 1x1 tr	1	on scar area	normal	normal	normal	normal	scar & 1x1 tr	8
scar		ant wall scar	normal	normal	scar	normal	normal	9
nil	nil	scar	normal	normal	normal	normal	scar	10
nil	nil	scar	normal	normal	normal	normal	normal	11
nil	nil	scar	normal	normal	normal	normal	normal	12
nil	nil	scar	normal	normal	normal	normal	normal	13
nil	nil	scar	normal	normal	normal	normal	normal	14
nil	nil	scar	normal	normal	normal	normal	normal	15
nil	nil	scar	normal	normal	normal	normal	scar	16
nil	nil	scar	normal	normal	normal	normal	scar	17
nil	nil	scar	normal	normal	normal	normal	scar	18
nil	nil	scar	normal	normal	normal	scar	normal	19
2x2cm scar & 1x1 tr	1	on scar	contracture	normal	normal	normal	normal	20
2x2 scar		scar	normal	normal	normal	scar	normal	21
4x3 scar	,	scar	normal	normal	normal	normal	normal	22
2x2 scar	,	scar	normal	normal	normal	scar	normal	23
2x2 scar	,	scar	normal	normal	normal	scar	normal	24
scar	1	rt lateral wall	normal	normal	normal	normal	normal	25
scar	,	rt lateral wall	normal	normal	normal	normal	normal	26
scar		post wall scar	normal	normal	normal	scar	normal	27

RT LAT	DIST Fm ORIFICE	APPEARANCE of scar	ASS. LESIONS	BIMANUALLY	RESECTION	Cx	MMC	BIOPSY	sno.
1x1	not involved	recurence on scars	multiple	not palpable	complete	nil	no	T1G3	1
3x3 r orifice	rt involved	recurence on scars	nil	not palpable	complete	nil	no	TaG3	2
normal	not involved	odematous	nil	not palpable	complete	nil	no	T1G3	3
normal	not involved	normal		not palpable	complete	nil	no	T2G3	4
scar + rec	involved	recurence on scars	nil	not palpable	complete	nil	no	TaG3	5
1x1 & .5x.5 on scar,	not involved	recurrence on scar	1	not palpable	complete	nil	no	TaG3	6
normal	not involved	recurrence	two	not palpable	complete	nil	no	TaG3	7
normal	not involved	recurrence	nil	not palpable	complete	nil	no	TaG3	8
normal	not involved	normal	nil	not palpable	complete	nil	no	T1G3	9
normal	scar	normal	nil	not palpable	complete	nil	No	no malignancy	10
scar	not involved	normal	nil	not palpable	complete	nil	No	no malignancy	11
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	12
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	13
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	14
scar	not involved	normal	nil	not palpable	complete	nil	No	no malignancy	15
normal	left orifice not seen - scar	odematous	nil	not palpable	complete	nil	No	no malignancy	16
normal	not involved	normal	nil	not palpable	complete	nil	No	no malignancy	17
normal	not involved	normal	nil	not palpable	complete	nil	No	no malignancy	18
normal	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	19
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	20
normal	involved	normal	nil	not palpable	complete	nil	no	no malignancy	21
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	22
normal	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	23
normal	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	24
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	25
scar	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	26
normal	not involved	normal	nil	not palpable	complete	nil	no	no malignancy	27

Bx STAGE	Bx GRADE	UP/DOWN STAGE
1	3	same
a	3	down
1	3	same
2	3	upstage
a	3	down
a	3	down
a	3	down
a	3	down
1	3	same
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
NA	NA	NA
na	na	na